Working Towards Alkaloid Macrocycles

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To Mam and Nana (without who this would not have been possible)

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of PhD in organic chemistry is entirely my own work, that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge breach any law of copyright, and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

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Working Towards Alkaloid Macrocycles

Brian Deegan

This thesis will describe the project carried out over the previous 3 years. In this project synthesis and isolation of new macrocyclic compounds containing 2-(2-hydroxyethoxy)phenol and a series of diacid dichlorides, both aromatic and aliphatic was achieved. The synthesis of an analogous set of macrocycles containing morphine in place of the 2-(2-hydroxyethoxy)phenol was attempted but unsuccessful.

The theory behind this plan was that the reactivity of the two hydroxy groups on the 2-(2-hydroxyethoxy)phenol and those on morphine will react in the same order. This gives the ability to selectively join two of the diol structures (morphine or 2-(2-hydroxyethoxy)phenol) through the phenolic hydroxy group using a diacid dichloride and then close these structures to make the macrocycles using another diacid dichloride. This method worked well for the 2-(2-hydroxyethoxy)phenol based macrocycles but did not work for the morphine containing macrocycles. A variety of other methods where attempted for the synthesis and isolation of the morphine macrocycles but they were not successfully isolated.

A sample of the compounds, both macrocyclic and the open structures, were tested for p-glycoprotein inhibition and also for toxicological screening against various bacterial species. From the results of this testing new compounds were designed, isolated and tested.

All of the compounds isolated where tested for metal binding to a selection of metals and this too will be reported on.

List Abbreviations

A

ABS	ATP binding site
ATP	Adenosine triphosphate

B

BnCl	Benzyl chloride
br.	broad

C

CAN	cerium(IV)ammonium nitrate

D

dba	dibenzylideneacetone
DCM	Dichloromethane
DI	D-ionised
DIPEA	*N*,*N*-Diisopropylethylamine
DLKP	human lung squamous carcinoma
DLKP-A	human lung squamous carcinoma, daughter cell line of DLKP in which an over-expression of P-gp occurs
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide

E

EDC (within schemes)	*N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide
EDC	enantiomer distribution constant (function of the concentration of the different enantiomers in the organic and the aqueous phases)
e.e.	enantiomeric excess
E_{homo}	Energy of highest occupied molecular orbital
eq.	equivalents

F

5FU	5-flourouracil

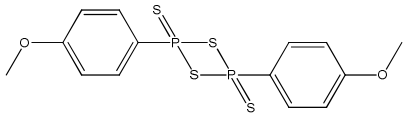
H

h	hour
HOBt	1-Hydroxybenzotriazole hydrate

K

$KOBu^t$	Potassium tert butoxide

L

Lawesson's reagent	
log P	Lipophilicity

M

MDR	multidrug resistance
MRP1	Multi-Drug Related Protein
MIC	Minimum inhibitory concentration
MRP1	Multidrug Resistance Associated Protein 1

N

ND	Not successfully determined
NEt_3	Triethylamine
NMO	4-methylmorpholine *N*-oxide
NMM	*N*-methylmorpholine
NEA	1-(naphthalen-1-yl)ethanamine

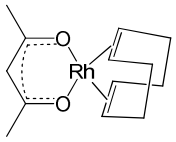
P

PPTS	*p*-Toluenesulfonic acid pyridine salt
PLE	Pig Liver Esterase
PEA	1-phenylethanamine
Pearlman's catalyst	$Pd(OH)_2/C$

P-gp	P-glycoprotein
PKCIs	protein kinase C inhibitors
PEG300	poly(ethylene)-glycol with average molecular weight of 300

R

RT	Room Temperature
Rh(COD)acac	(Acetylacetonato)(1,5-cyclooctadiene)rhodium(I)



RT	Room Temperature
R_f	Retardation factor

S

spp.	species
sp.	species
SBHR	steroid-binding hydrophobic region

T

TBDMSCl (*t*-BDMSCl)	*tert*-Butyldimethylchlorosilane
THF	tetrahydrofuran
TBAF	Tetrabutylammonium fluoride
TPAP	tetrapropylammonium peruthenate
$TBAHSO_4$	Tetrabutylammonium bisulphate
TBDPS	*tert*-butyldiphenylsilyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid

V

v.br.	very broad

Z

Z	benzyloxycarbonyl

Chapter 1

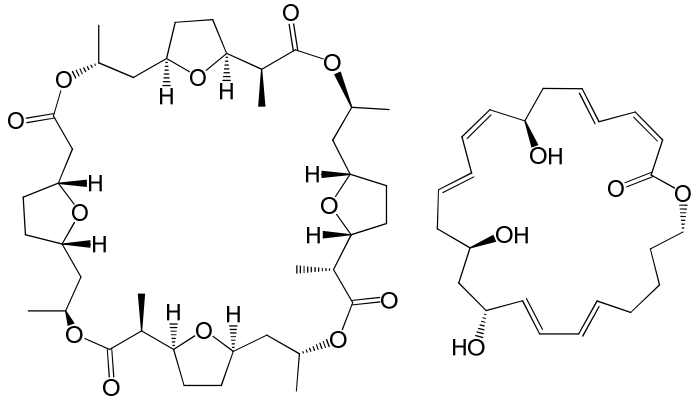
Literature Review

1.1 Chiral Crown ethers

1.1.1 Naturally Occurring Chiral Crown Ethers

Crown ethers contain a series of carbon units, alkyl or aromatic, linked by oxygen atoms. Lone pairs on oxygen can be used in binding of the crown to cations. The cations can be metallic or non-metallic such as protonated amines. Crown ethers are defined mainly by their shape, with the oxygen atoms forming the base of the crown and each of the carbon units being the points on the crown.

Crown ethers are studied for different reasons ranging from their biological activity[1] to catalysis[2] and utilisation in sensors.[3] All of these applications stem from their structure, which provides them with natural cavities suitable for a huge variety of functions, including antibacterial agents[4] and sensors.[3] Crown ether chemistry is a highly dynamic field of research with new crown ethers are constantly being developed and their properties investigated.[5] Some chiral crown ethers have been synthesised as racemic mixtures or in very small enantiomeric excess (e.e.), and then require separation of the stereoisomers. Separation of enantiomers is very difficult as they share many of the same chemical and physical properties. One method to overcome this problem is to synthesise enantiomerically pure macrocycles. There are many examples of biologically active chiral crown ethers, including Nonactin, **1**, Macrolactin A, **2**, and Monensin B. Nonactin and Macrolactin A are naturally occurring molecules and have been studied by several natural product isolation and total synthesis groups.

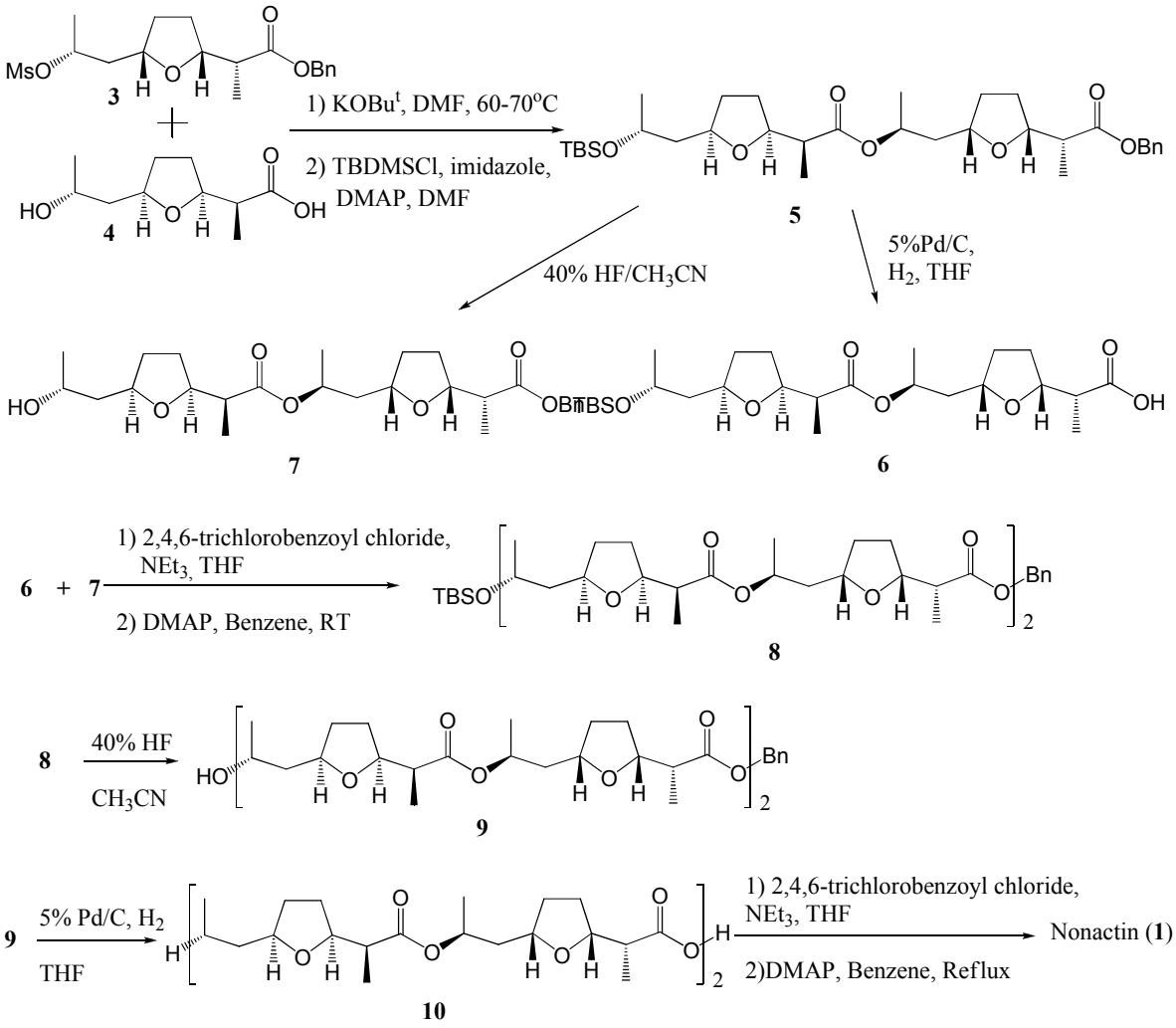


1: Nonactin

2: (–)-Macrolactin A

Figure 1: Structures of **1** *and* **2**.

Nonactin is the lowest homologue of the family of macrotetrolide antibiotics that have been isolated from a variety of *streptomyces* cultures. Nonactin has been successfully synthesised without the use of biological reagents (bacteria, enzymes, fungi etc.) by Lee in 1996.[6]



Scheme 1: Synthesis of Nonactin **1**

Lee's synthesis is extensive, with ten synthetic steps to prepare **4** and eleven steps to synthesise **3**, the starting materials for the synthesis. This is followed by a further eight steps to synthesise Nonactin (**1**) (scheme 1). Lengthy (many step) reactions have major drawbacks. For example, a small decrease in yield at each step will overall give rise to a moderate to low yield. Also after each step if purification is not carried out the unwanted products from each step can undergo competing reactions in the following steps which leads to many impurities which can make the final purification very difficult. Nonactin is known as being a potent antibacterial.[7] The structure of Nonactin,

as with many crown ethers, means that it acts as an ionophore. Nonactin has been proven effective against Gram positive bacteria, mycobacteria and fungi.[7]

Another example of a naturally occurring chiral crown ether that has been synthesised in the laboratory is (–)-Macrolactin A, **2**, by Jarosz *et al.*[8] Macrolactin A exhibits a broad band of activity with significant antiviral and cancer cell cytotoxic properties and also has implications for controlling human HIV.

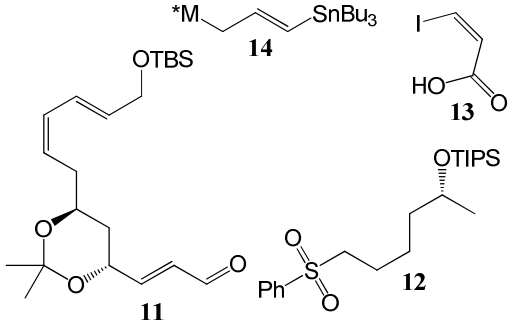
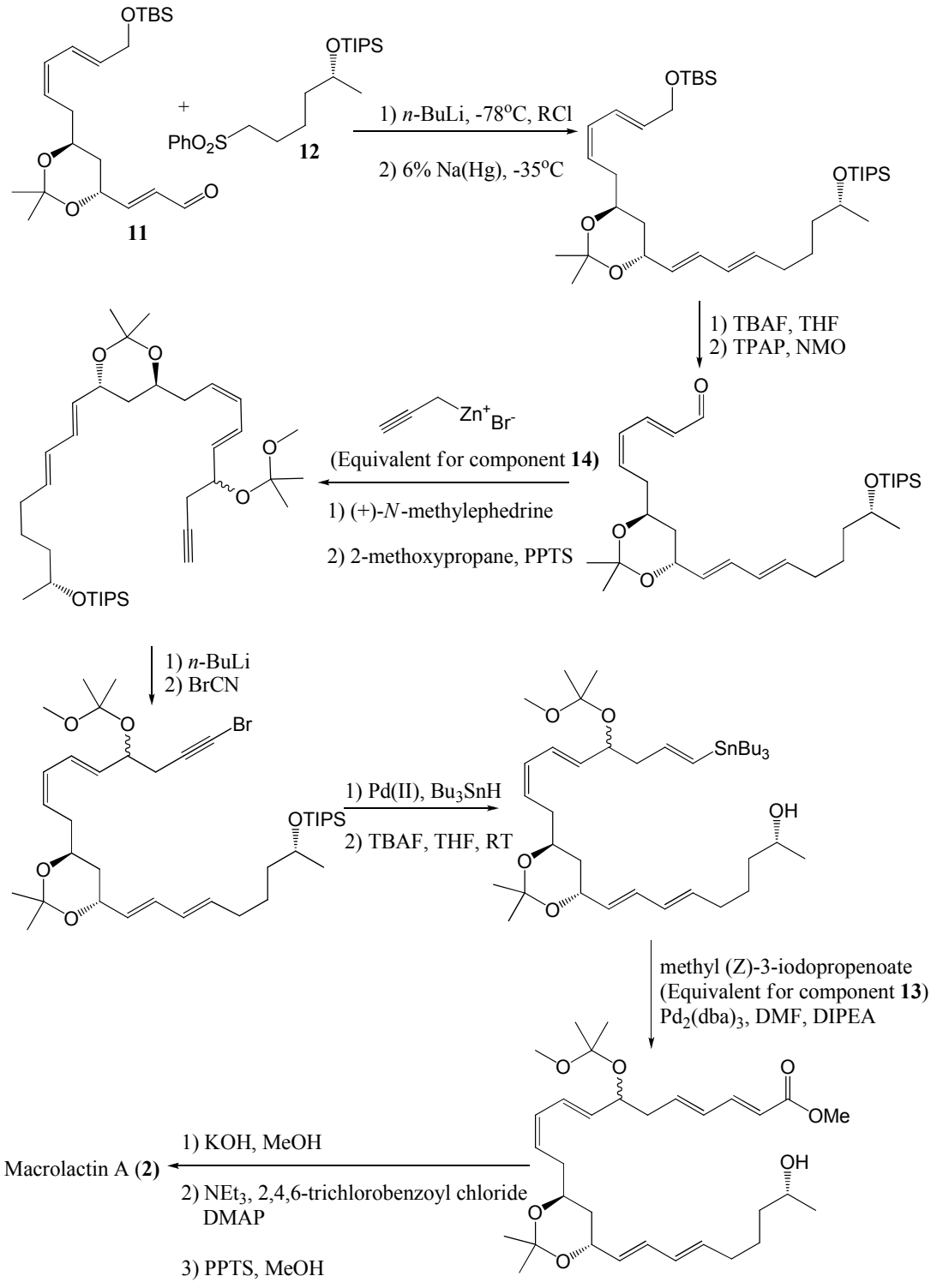


Figure 2: The principal components for synthesis (–)-Macrolactin A

The synthesis of **2** was carried out using four principal components (**11**, **12**, **13** and **14**) in thirteen steps from principle components and provides relatively low yields of product. Although each step in the reaction proceeds in high yields, with the exception of the cyclisation (26 %), there are thirteen steps in the synthesis resulting in a low overall yield (1.9 %).



Scheme 2: Synthesis of (-)-Macrolactin A, **2**

The overall yield increases to 5.1 % if the synthesis of the 4 principal components (**11**, **12**, **13** and **14**) is not taken into account. Although this synthesis is successful the method is complicated with thirteen synthetic steps from principal components to the finished product.

Nigericin, **15,** is a polyether which is available by fermentation of *streptomyces sp*. Although the structure is a linear (figure 3) configuration it has been shown to normally exist in a circular shape with head to tail hydrogen bonding between the terminal carboxylic acid and the terminal alcohol group.[9]

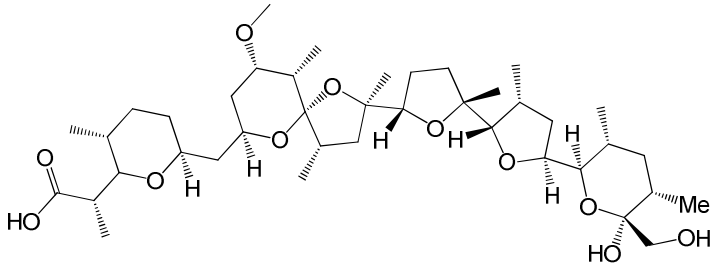
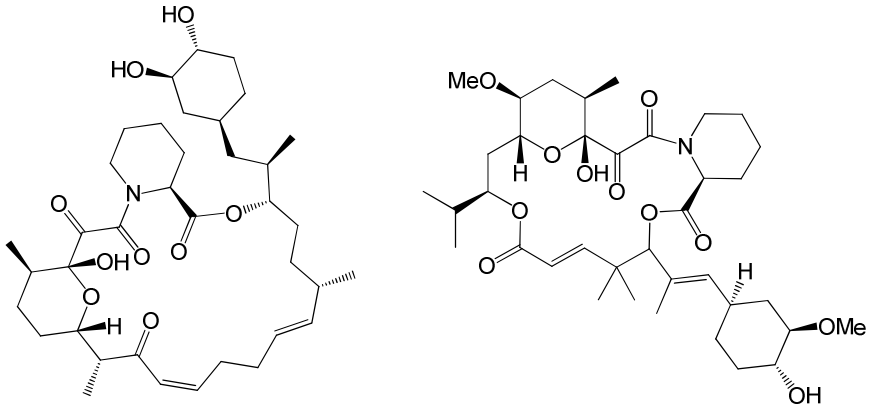


Figure 3: Nigericin, **15**

Although this compound is not a crown ether it shares many of the properties of the crown ethers, i.e. it is a polyether ionophore and on complexation with a guest species it wraps around the guest forming the crown shape, with the oxygen atoms donating electron density to the cation guest species. Nigericin has not been synthesised successfully but some subunits have been prepared, e.g. the tetrahydropyran subunit.[10] It is currently being used as an antibiotic and is a highly active K^+ and Pb^+ ionophore. Nigericin is being considered as a treatment for Pb intoxication.[11]

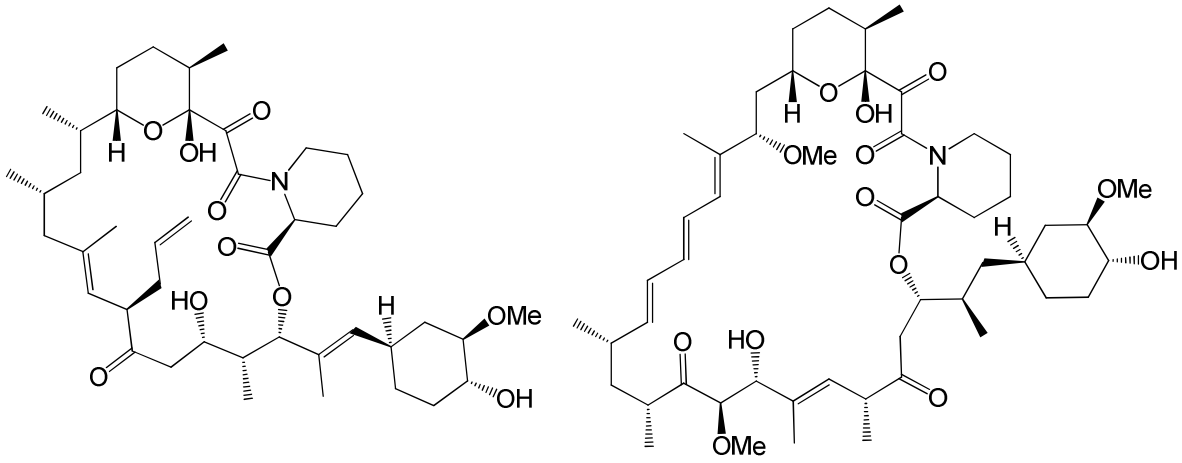
Another natural occurring chiral macrocycle is antascomicin A, (figure 4) which is produced by a strain of *Micromonospora n. sp*. A92-306401.[12] Also shown in figure 4 is 506BD, a synthetic variation of antascomicin A[13] which has been synthesised in twenty-six steps with an overall yield of 0.23%. Both of these macrocycles are potent binders to FKBP12, and do not interfere with T-cell activation. They are both immunosuppressants and also inhibit the immunosuppressant activity of FK506 (tacrolimus, **18**) and rapamycin (**19**). Structures of **18** and **19** are given in figure 5.



16: Antascomicin A **17**: 506BD

Figure 4: Antascomicin A and the synthetic variation 506BD

Both FK506 (tacrolimus) and rapamycin bind to FKBP12 and inhibit distinct signal transduction pathways in the T lymphocyte.[13] Tacrolimus is produced by *Streptomyces tsukubaensis* and rapamycin is produced by *Streptomyces hygroscopicus.*[14]

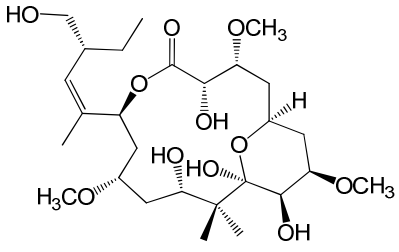


18: Tacrolimus **19**: Rapamycin

Figure 5: Tacrolimus and Rapamycin

Tacrolimus and rapamycin are both immunosuppressive and of interest for cancer therapies. If antascomicin A and 506BD inhibit the immunosuppressant activity of tacrolimus and rapamycin then it is possible to find other compounds that will also inhibit the activity. As a consequence of this, both tacrolimus and rapamycin may become more interesting for cancer therapies, as they will not have the side-effects of being an immunosuppressant for the cancer patient.

In 2000 West *et al.* reported the isolation and characterisation of peloruside A, **20** (figure 6), which is a potent cytotoxic macrolide from the New Zealand marine sponge *mycale sp.*[15] In 2008 Richard E. Taylor *et al.* published a review of the synthetic efforts in the successful synthesis of this macrocycle.[16]



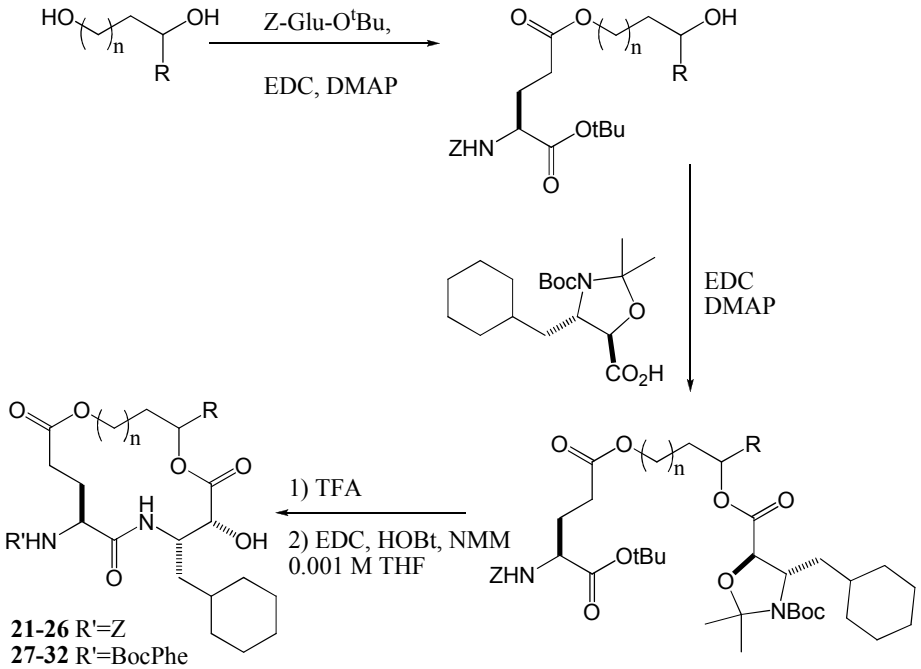
20

Figure 6: (+)-Peloruside A

Previously, a report proclaimed peloruside A as a potent cytotoxic agent with paclitaxel-like microtubule-stabilizing activity[17] and has also been shown to have

synergistic effects with taxoid site drugs including Taxol®, epothilone, discodermolide and eleuthorobin.[18]

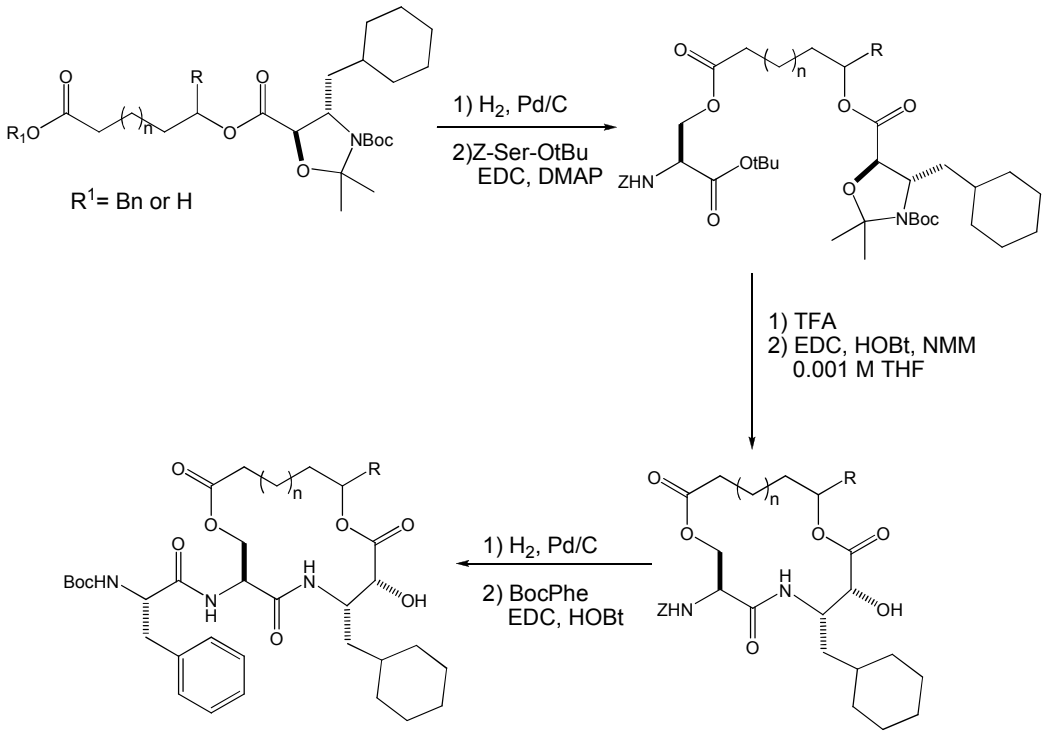
Weber *et al.* published the synthesis and biological data of fifty-six chiral macrocycles.[19] These are not naturally occurring species but are derived from natural products. **21**-**32** are glutamate derived macrocycles and **33**-**76** are serine derived macrocycles. The synthesis of these macrocycles is shown in schemes 3 and 4.



21-26 R'=Z
27-32 R'=BocPhe
21, 27 n=0 R=H
22, 28 n=1 R=H
23, 29 n=0 R=*n*Bu Diastereomer 1
24, 30 n=0 R=*n*Bu Diastereomer 2
25, 31 n=0 R=$CH_2N(CH_2CH_2)_2O$ Diastereomer 1
26, 32 n=0 R=$CH_2N(CH_2CH_2)_2O$ Diastereomer 2

Scheme 3: Synthesis of Macrocycles **21**-**32**

21-**26** underwent hydrogenation with palladium/carbon catalyst followed by addition of the BocPhe group in the presence of EDC and HOBt to produce **27**-**32**.



55: n=0, R=H, diastereomer 1
56: n=1, R=H, diastereomer 1
57: n=1, R=*n*Bu, diastereomer 1
58: n=1, R=*n*Bu, diastereomer 2
59: n=0, R=*i*Bu, diastereomer 1
60: n=0, R=*i*Bu, diastereomer 2
61: n=1, R=*i*Bu, diastereomer 1
62: n=1, R=*i*Bu, diastereomer 2
63: n=0, R=neopentyl, diastereomer 1
64: n=0, R=neopentyl, diastereomer 2
65: n=1, R=neopentyl, diastereomer 1
66: n=1, R=neopentyl, diastereomer 2
67: n=0, R=$CH_2N(CH_2CH_2)O$, diastereomer 1
68: n=0, R=$CH_2N(CH_2CH_2)O$, diastereomer 2
69: n=1, R=$CH_2N(CH_2CH_2)O$, diastereomer 1
70: n=1, R=$CH_2N(CH_2CH_2)O$, diastereomer 2
71: n=1, R=$CH_2NHCO_2CH_2CCl_3$, diastereomer 1
72: n=1, R=$CH_2NHCO_2CH_2CCl_3$, diastereomer 2
73: n=1, R=CH_2NMe_2, diastereomer 1
74: n=1, R=CH_2NMe_2, diastereomer 2
75: n=1, R=CH_2NEt_2, diastereomer 1
76: n=1, R=CH_2NEt_2, diastereomer 2

33: n=0, R=H, diastereomer 1
34: n=1, R=H, diastereomer 1
35: n=1, R=*n*Bu, diastereomer 1
36: n=1, R=*n*Bu, diastereomer 2
37: n=0, R=*i*Bu, diastereomer 1
38: n=0, R=*i*Bu, diastereomer 2
39: n=1, R=*i*Bu, diastereomer 1
40: n=1, R=*i*Bu, diastereomer 2
41: n=0, R=neopentyl, diastereomer 1
42: n=0, R=neopentyl, diastereomer 2
43: n=1, R=neopentyl, diastereomer 1
44: n=1, R=neopentyl, diastereomer 2
45: n=0, R=$CH_2N(CH_2CH_2)O$, diastereomer 1
46: n=0, R=$CH_2N(CH_2CH_2)O$, diastereomer 2
47: n=1, R=$CH_2N(CH_2CH_2)O$, diastereomer 1
48: n=1, R=$CH_2N(CH_2CH_2)O$, diastereomer 2
49: n=1, R=$CH_2NHCO_2CH_2CCl_3$, diastereomer 1
50: n=1, R=$CH_2NHCO_2CH_2CCl_3$, diastereomer 2
51: n=1, R=CH_2NMe_2, diastereomer 1
52: n=1, R=CH_2NMe_2, diastereomer 2
53: n=1, R=CH_2NEt_2, diastereomer 1
54: n=1, R=CH_2NEt_2, diastereomer 2

Scheme 4: Synthesis of Macrocycles **33-76**

27-**32** and **55**-**76** showed activity towards the inhibition of human plasma renin. Renin is used by the body to help regulate blood pressure and so by controlling the activity of renin in the body some manipulation of blood pressure can be achieved. In the glutamate derived series (**27**-**32**) the thirteen membered ring structure (**27)** was more active as an inhibitor of renin than the fourteen membered analogue (**28**). In the serine derived series the fourteen membered rings were more active than the thirteen membered analogues, for example **65** was more active than **63.** In both the glutamine and serine derived series where R≠H, **35**-**54** and **57**-**76**, one diastereomer is invariably more active than the other, although which diastereomer is the more active depends on

the substituent. For example **30** was three times as active as its diastereomer **29** but **31** was over a thousand fold more active than its diastereomer **30**.

1.1.2 Chiral 18-Crown-6 Ethers

A review published in 1997[20] compiled five rules to be considered when designing chiral macrocycles as enantioselective host molecules. These rules were brought together with reference to enantiomeric recognition of amines but may apply to any chiral guest molecule. The rules are listed here:

1) "*in order to obtain effective enantiomeric recognition, a primary requirement is that chiral macrocyclic receptors form reasonably stable complexes with guest enantiomers so that the repulsive interactions can effectively lessen the stability of the complex of one enantiomer*":

2) *"the larger chiral barrier(s) of a macrocycle usually results in a larger degree of enantiomeric recognition*"

3) "*The low conformational flexibility of diastereomeric complexes results in a high degree of enantiomeric recognition. Such limited conformational flexibility usually results from the rigidity of the macrocycles and the possibility of multipoint attractive interactions between host and guest molecules"*

4) "*In order to have a high degree of enantiomeric recognition, the chiral macrocyclic compound should be stereochemically complementary with the guest enantiomers*"

5) "*The macrocyclic receptors possessing C2, C3, and D2 symmetry show higher enantioselectivity than those of C1 and D3 symmetry*".

The first rule for enantiomeric recognition requires that macrocycles must have the ability to bind to the target guest molecule. This basic requirement is the most important. If the host molecule (the macrocycle) cannot bind to the guest molecule it will not have the ability to distinguish between the enantiomers of the guest.

The second rule means that as the bulkiness of the chiral substituent(s) increase the enantioselectivity of the chiral macrocycle will increase. This occurs because the large group will stericaly hinder binding of the unfavourable enantiomer. Also with this rule there is an upper limit. If the group is so large that it blocks the binding of the guest then enantiomeric recognition will be decreased. The maximum size the substituent at the chiral centre can be before a negative impact on enantiomeric recognition occurs is related to the size of the macrocycle and the target guest molecule.

The third rule specifies the lower the conformational flexibility of the macrocycle, the stronger the enantiomeric recognition will be. This indicates that if the macrocycle is rigid then its conformation will be unable to adjust to fit both enantiomers, e.g. if the macrocycle is rigid and binds to the *S* enantiomer strongly it will be unable to adjust enough to accommodate the *R* enantiomer leading to a weak binding of the *R* enantiomer.

The fourth rule relates to stereochemical complementarity, this means that the structures of the host and target guest molecule should complement each other both structurally and chemically. In the host guest complex where the host molecule and guest molecule are in close proximity there should be groups which attract each other to strengthen the binding in the complex. Also any groups on either the guest or host that could hinder the binding in the guest to host should not interact at the binding site.

The fifth rule states that macrocyclic receptors possessing C2, C3, and D2 symmetry show higher enantioselectivity than those of C1 and D3 symmetry. C1 symmetric macrocycles have limited steric hindrance to provide an effective chiral environment for enantiomer recognition. D3 symmetric macrocycles have the same chiral substituents in triplicate; one substituent is in each section of the macrocycle. This means that if one enantiomer can bind to the macrocycle, the other enantiomer will also bind to a similar extent.

In 1991 four chiral 18-crown-6 ethers, **77, 78, 79** and **80**, were synthesised using cyclohexane-1,2-diol derivatives as the source of chirality.[21]

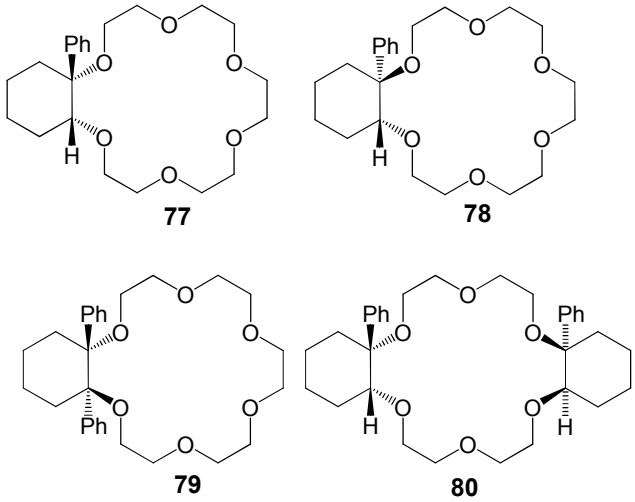
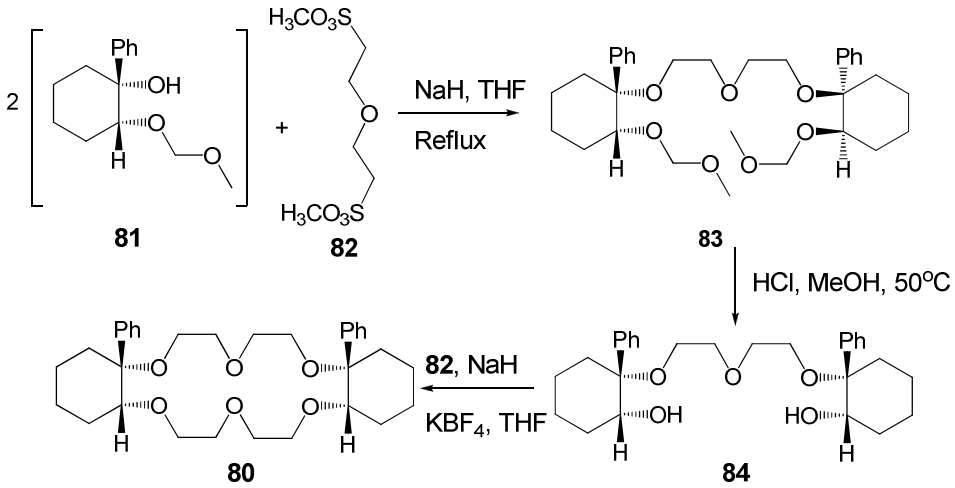


Figure 6: Compounds **77, 78, 79** and **80**

Pig liver esterase (PLE) was used as the catalyst in the synthesis of the chiral cyclohexane-1,2-diols because PLE gave higher optical purity and was less

complicated than the chemical method. The three macrocycles that only contain one cyclohexane-1,2-diol, structures **77**, **78** and **79**, were synthesised by the reaction (under reflux conditions in THF) of the appropriate cyclohexane diol with pentaethyleneglycol *bis*(toluene-*p*-sulphonate) in the presence of NaH and KBF_4. This gave yields ranging from 15 % to 62 %.



Scheme 5: Synthesis of **80**

Cis-cyclohexane-1,2-diol was treated with dimethoxymethane, LiBr and toluene-*p*-sulphonic acid to isolate **81**. The synthesis of **80,** 27 % yield, from **81** to the macrocycle is outlined in scheme 3. Chiral crown ethers, **77**-**80**, have been tested for transport of chiral compounds through bulk liquid membranes, using two racemic guest species, 1,2-diphenylethylamine hydrochloride and methyl phenylglycinate hydrochloride. **79** and **80** show high enantiomeric selectivity for (*S*)-1,2-diphenylethylamine with optical purities of 81 % and 70 %, respectively, being obtained. This indicates that at least two phenyl units are required on these macrocycles to act as a significant chiral steric barrier for the guest species tested.

In 1995 Peiffer *et al.* synthesised four chiral 18-crown-6 ethers, **85, 86, 87** and **88**, using chiral glycols, which were obtained from the α–amino acids: L-valine, L-leucine, L-isoleucine and L-phenylalanine.[22]

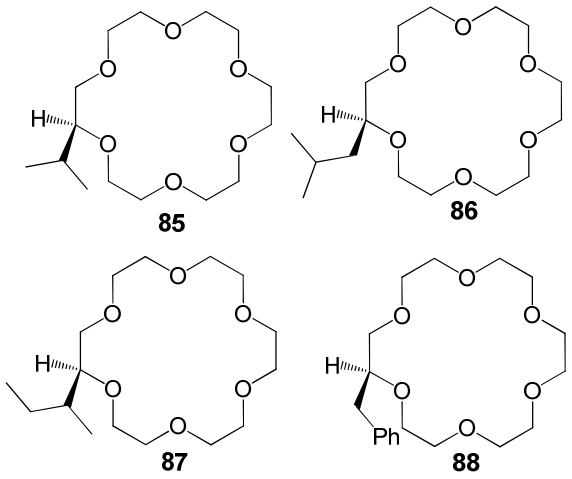


Figure 7: Compounds **85**-**88**

Crown ethers **85**-**88** were synthesised in two steps from the amino acid starting material. First the amino acids were converted to the corresponding chiral glycol by reaction with sodium nitrate/acetic acid and lithium aluminium hydride in tetrahydrofuran. Pentaethyleneglycol *bis*(toluene-*p*-sulphonate) underwent a condensation reaction with the glycol to give the four chiral crown ethers in yields from 28 % to 45 %. **85**-**88** were tested for the extraction of a number of radioelements both of α–emitting elements (Mn 54, Co 60, Sr 85, Cs 137 and Eu 152) and γ–emitting elements (Pu 231, Np 237 and Am 241). **85**-**88** gave positive results for the extraction of the actinides, although they were less efficient at extracting the actinides as the most commonly used extractant [(*N*,*N*-diisoprpyl) octo phenyl carbamoylmethylphosphine oxide] and were limited in their ability to extract both the alkaline earth metals and transition metals.

Sharma produced a series of chiral 18-crown-6 ethers from *D*-xylose.[23] This was attained in four to six steps from a *D*-xylose derivative, yielding four different chiral crown ethers in yields from 4 % to 9 %. Each of these crown ethers, **89**-**92**, has eight chiral centres in their structures shown in figure 8.

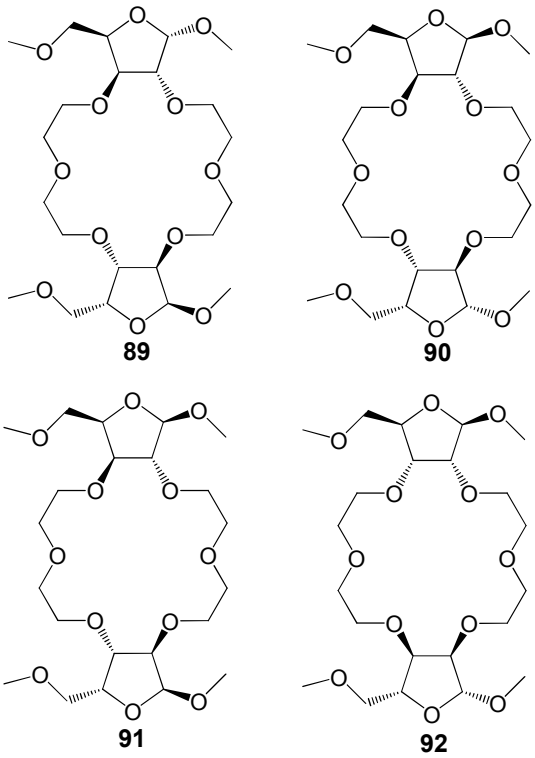
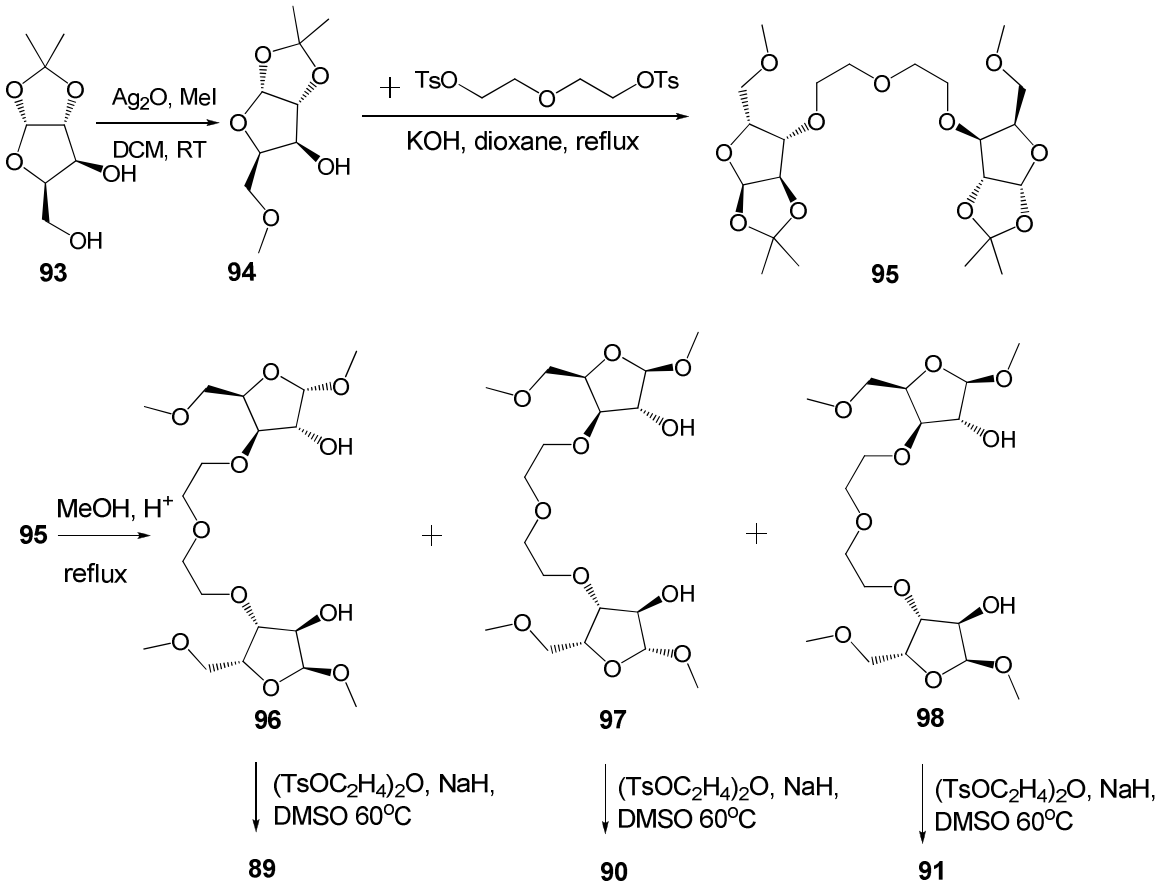


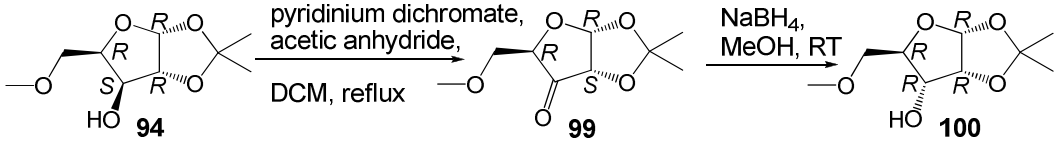
Figure 8: Crown ethers **89**-**92**

89-**91** were synthesised using the four step method outlined in scheme 4 from starting material, **93**. Deprotection of the acetonide group in **95** yielded a mixture of three intermediates, **96**, **97** and **98**. **96**, **97** and **98** underwent condensation with diethyleneglycol ditosylate in the presence of sodium hydride in dimethylsulphoxide, to furnish the chiral 18-crown-6 ethers **89**, **90** and **91**.



Scheme 6: synthesis of crown ethers **89**, **90** *and* **91**

93 was treated with silver oxide and methyl iodide in dichloromethane at room temperature to produce **94**, which underwent oxidisation with pyridinium dichromate and acetic anhydride in dichloromethane to produce **99**. **99** was subjected to reduction with sodium borohydride to produce the *ribo* derivative, **100**.



Scheme 7: Synthesis of **100**.

Using **100** (in place of **94**) the same reaction pathways was followed (scheme 6) producing the macrocycle product, **92**.

In 2002 Yamato *et al.* reported the synthesis of chiral 18-crown-6 ethers, **105r** and **105s**, using stereoisomers of cyclohexane-1,2-diol. Their stability constants for potassium complexation in methanol in comparison to previously reported isomers **101**-**104**[24] were also communicated.

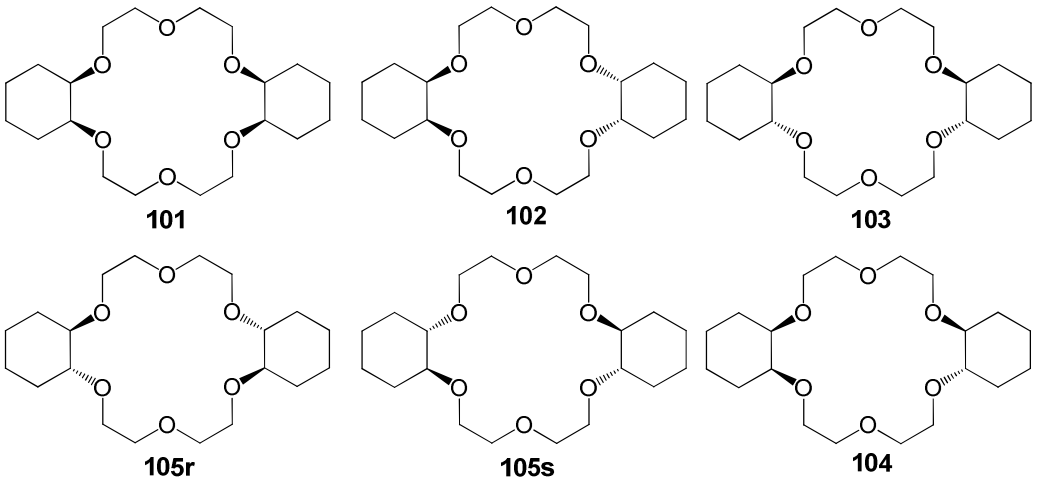
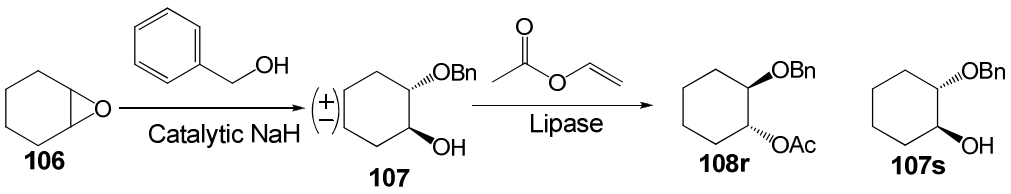


Figure 9: Structures of Compounds **101**-**105**

Cyclohexene oxide, **106**, was reacted with benzyl alcohol with a catalytic amount of NaH. This reaction results in a racemic mixture of *trans*-2-benzyloxycyclohexanol **107**, which is then acetylated using lipase enzyme.



Scheme 8: Synthesis of **108r** *and* **107s**

The lipase enzyme acetylated the (*R*)-alcohol producing the (*R*)-acetate (**108r**). **108r** and (*S*)-alcohol (**107s**) were separated and **108r** was hydrolyzed yielding the (*R*)-alcohol **107r**, thus enabling the enantiomers (**107r** and **107s**) to be separated with an enantiomeric excess > 95 %. **107r** and **107s** were reacted with diethyleneglycol ditosylate followed by the removal of the benzyl groups by hydrogenation using Pd-C catalyst. The resulting diols were reacted with another equivalent of diethyleneglycol ditosylate to give the 18-crown-6 products **105s** and **105r**. **101**-**105** have been shown to have stability constants for K^+ (log Ks) complexation in methanol at 25 °C of: **101**) 5.88; **102**) 5.33; **103**) 4.08; **104**) 4.53; **105**) 3.10,[25] which show that the greater the number of *cis* cyclohexane rings in the crown ethers in this group the better the binding to potassium.

Colera *et al*. synthesised six chiral 18-crown-6 ethers, **109-114**, (figure 10) with lipophilic side chains.[26] Three complexes (**110**, **112** and **114**) have benzyl groups at the end of the lipophilic side chains and three complexes (**109**, **111** and **113**) have the benzyl groups removed.

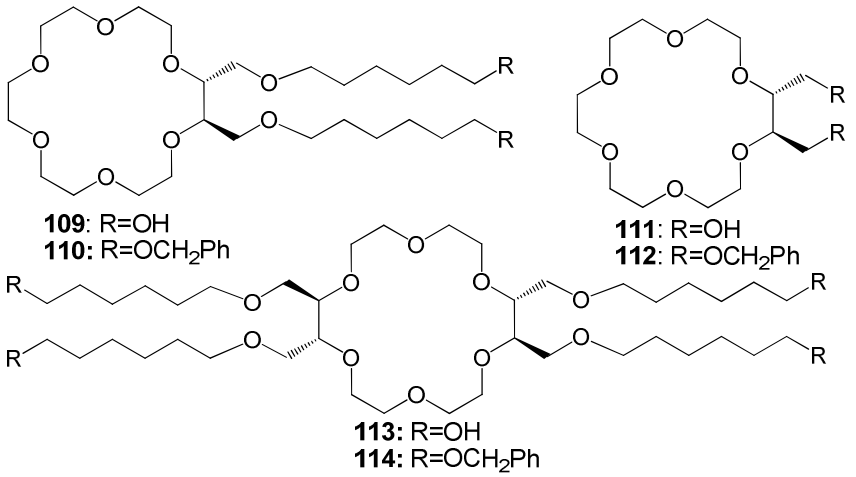
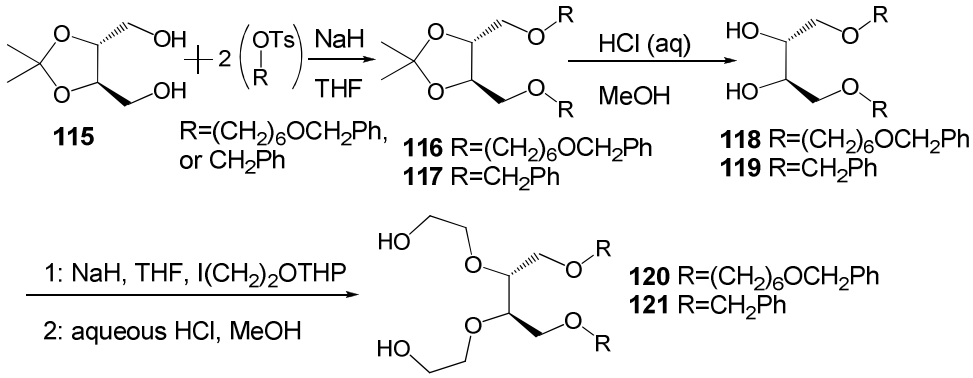


Figure 10: Structure **109**-**114**

(–)-2,3-*O*-Isopropylidene-*D*-threitol, **115**, was used as the chiral starting material in the synthesis of **109**-**114**. **115** was alkylated or benzylated yielding **116** and **117** respectively, with **118** and **119** being prepared from **116** and **117** respectively via acid hydrolysis.



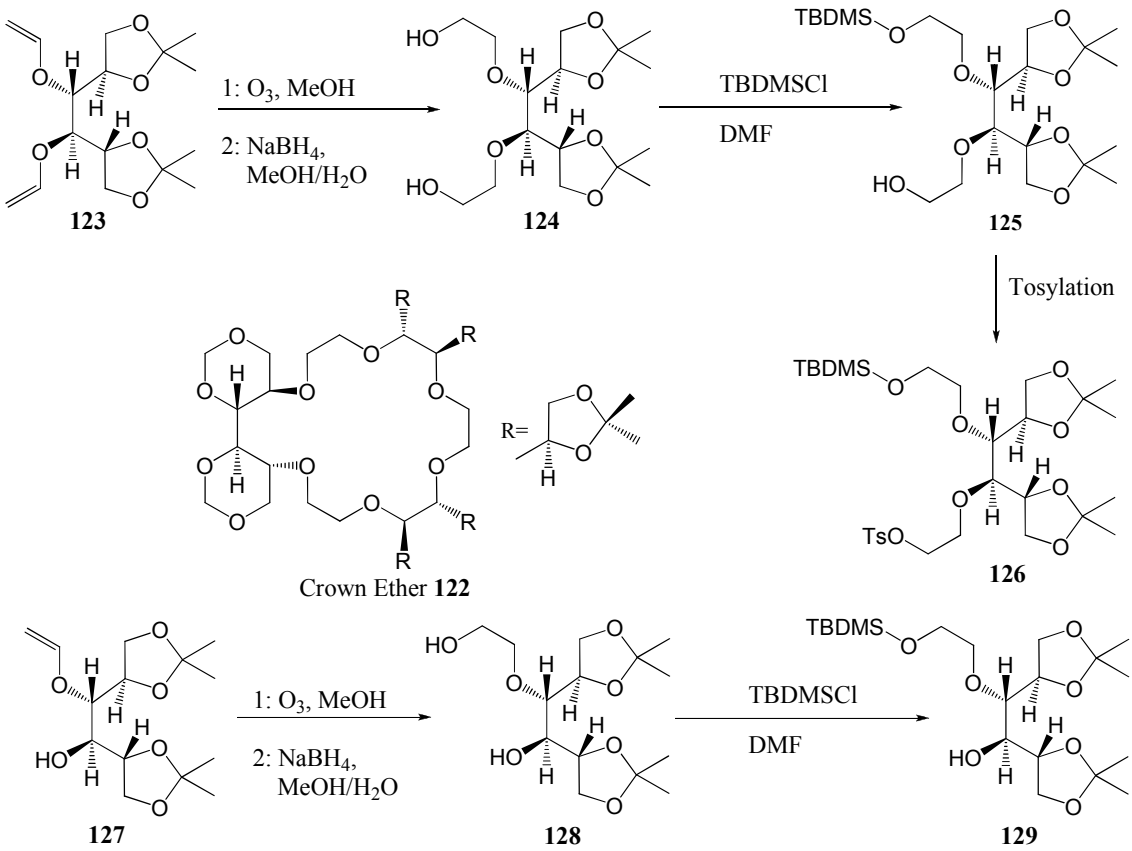
Scheme 9: Synthesis of **120** *and* **121**

Diols, **118** and **119** were alkylated with 2-(2-iodoethoxy)tetrahydro-*2H*-pyran followed by the removal of the tetrahydropyran moiety furnishing **120** and **121** respectively. **120** and **121**, were each reacted with triethylene glycol *di*-*O*-tosylate to form the crown ethers **110** and **112** respectively. For the preparation of **114**; **120** was mesylated and the mesylated product was reacted with another equivalent of **120**. Each of the crown ethers, **110**, **112** and **114**, were hydrolysed to give crown ethers **109**, **111** and **113** respectively. **109**-**114** underwent complexation studies, their complexation constants were measured by ^{1}H-NMR studies in CD_3CN with two chiral alkylammonium picrates, *sec*-butylammonium picrate and *α*-methylbenylammonium picrate. From the studies carried out **109** and **110** both show good binding to the alkylammonium picrates and also exhibit enantiomeric recognition. **109** binds preferentially to *R*-*sec*-butylammonium picrate over the *S* enantiomer with Log *K* values of 4.61 and 2.55

respectively and binds preferentially to *R*-*α*-methylbenylammonium picrate over the *S* enantiomer with Log *K* values of 5.42 and 2.24 respectively. **110** binds preferentially to *R*-*sec*-butylammonium picrate over the *S* enantiomer with Log *K* values of 4.91 and 2.27 respectively and binds preferentially to *R*-*α*-methylbenylammonium picrate over the *S* enantiomer with Log *K* values of 5.08 and 2.65 respectively. **111**-**114** did not exhibit significant binding to the picrates nor significant enantiomeric recognition. This suggests that the presence of two lipophilic chains gave rise to the best conditions for both binding to the desired alkylammonium picrates and also for the enantiomeric recognition.

1.1.3 Chiral Crown Ethers of Different Ring Sizes

Chiral 20-crown-6 ether, **122**, has been synthesised containing three carbohydrate residues.[27] **122** was synthesised in eight steps from diacetone-*D*-mannitol. Diacetone-*D*-mannitol was allylated producing ethers **123** and **127**. **123** and **127** were separated and individually underwent ozonolysis followed by reductive work up to yield diol products **124** and **128** respectively. **124** and **128** were protected using one equivalent of *tert*-butyldimethylsilyl chloride producing **125** and **129** respectively.



*Scheme 10: Synthesis of **126** and **129** and structure of **122***

125 was tosylated in near quantitative yield affording **126**, which was reacted with **129** to form a longer chain with ^{t}butyldimethylsilyl protecting groups at both ends. Deprotection then tosylation of both alcohol groups, followed by condensation reaction with (4*R*,4'*R*,5*R*,5'*R*)-4,4'-bi(1,3-dioxane)-5,5'-diol produced **122**.

Naemura *et al.* has reported the synthesis of two chiral crown ethers **130** and **131** using *cis*-4b,5,6,10b,11,12-hexahydrochrysene and *cis*-4b,5,9b,10-tetrahydroindeno[2,1-a]indene, respectively (figure 11).[28]

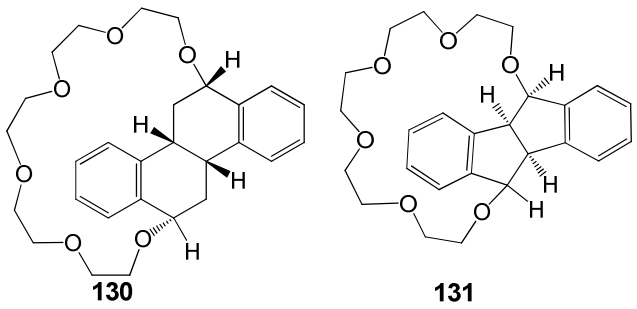


*Figure 11: structures of Crown ethers **130** and **131***

The subunit *cis*-4b,5,9b,10-tetrahydroindeno[2,1-a]indene was reported in 1980 by Ogura *et al.*[29] and *cis*-4b,5,6,10b,11,12-hexahydrochrysene was reported by Ramage *et*

al. in 1933.[30] The reaction of *cis*-4b,5,6,10b,11,12-hexahydrochrysene with pentaethyleneglycol ditosylate in a mixture of sodium hydride and tetrahydrofuran produced **130** in 57 % yield. The same methodology using *cis*-4b,5,9b,10-tetrahydroindeno[2,1-a]indene, in place of *cis*-4b,5,6,10b,11,12-hexahydrochrysene, provides the macrocycle **131** in 50 % yield. **130** and **131** were tested for enantiomeric recognition with 1,2-diphenylethylamine, 2-aminotetralin and methylphenylglycinate hydrochloride. The results show that **131** had better enantiomeric recognition than **130** out of the two guest species, which signifies that the more rigid the subunit contained in these crown ethers the better the enantiomer recognition is for these particular guest species.

In 1989 Kataky *et al.* synthesised a series of chiral 14-crown-4 ethers, **132**-**143**, with the structures shown in figure 12.[31]

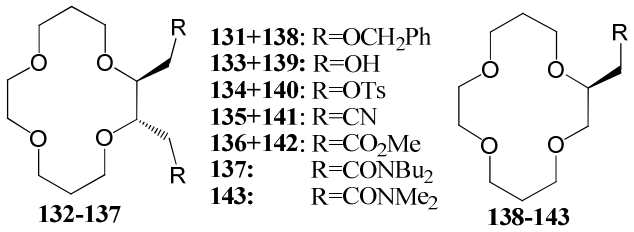
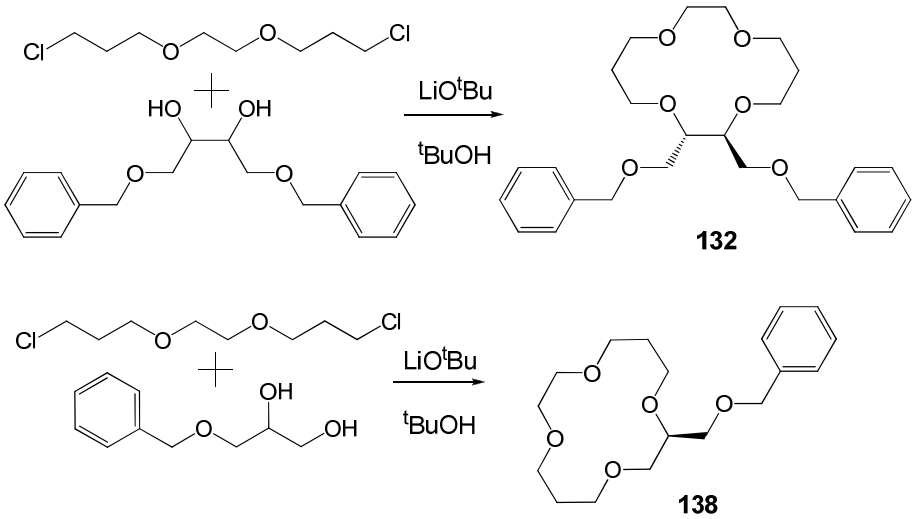


Figure 12: Crown ethers **132**-**143**

1,10-Dichloro-4,7-dioxadecane reacted with (*S*)-1,4-*bis*(benzyloxy)butane-2,3-diol in the presence of lithium *t*-butoxide in *t*-butanol producing the disubstituted ether (**132**, scheme 11) in 51 % yield. 1,10-Dichloro-4,7-dioxadecane and 3-(benzyloxy)propane-1,2-diol were used under the same methodology producing the monosubstituted ether (**138**, scheme 11) with the yield being unreported.



Scheme 11: Synthesis of ethers **132** *and* **138**

Hydrolysis was carried out on **132** and **138** removing the benzyl groups yielding ethers **133** and **139**. **133** and **139** were then tosylated yielding crowns **134** and **140**. Substitution of the tosylate groups on **134** and **140** with nitrile groups produced **135** and **141.** Methanolysis on **135** and **141** gave the methyl esters **136** and **142**. The methyl esters, **136** and **142**, were converted to acid chlorides with phosphorous pentachloride in dichloromethane. The acid chloride of the disubstituted 14-crown-4 ether was then reacted with *N*,*N*-dibutylamine to form the *bis*-*N*,*N*-dibutylamide product, **137**. The acid chloride of the single substituted 14-crown-4 ether was reacted with *N*,*N*-dimethylamine to make the *N*,*N*-dimethylamide product, **143**. These macrocycles were tested for Li^+ selectivity in blood serum mimicking solution. The disubstituted *bis*-*N*,*N*-dibutylamide crown ether proved best and superior to previously reported systems.

A series of crown ethers have been synthesised using 1-phenylethane-1,2-diol and 2,4-dimethyl-3-oxapentane-1,5-diol as chiral subunits, **144**-**147**.[32]

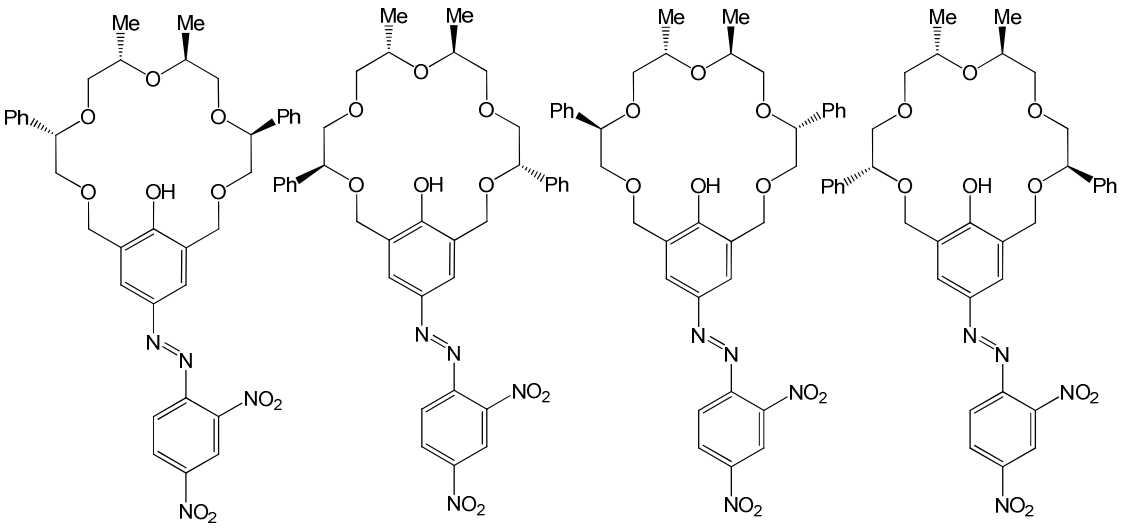
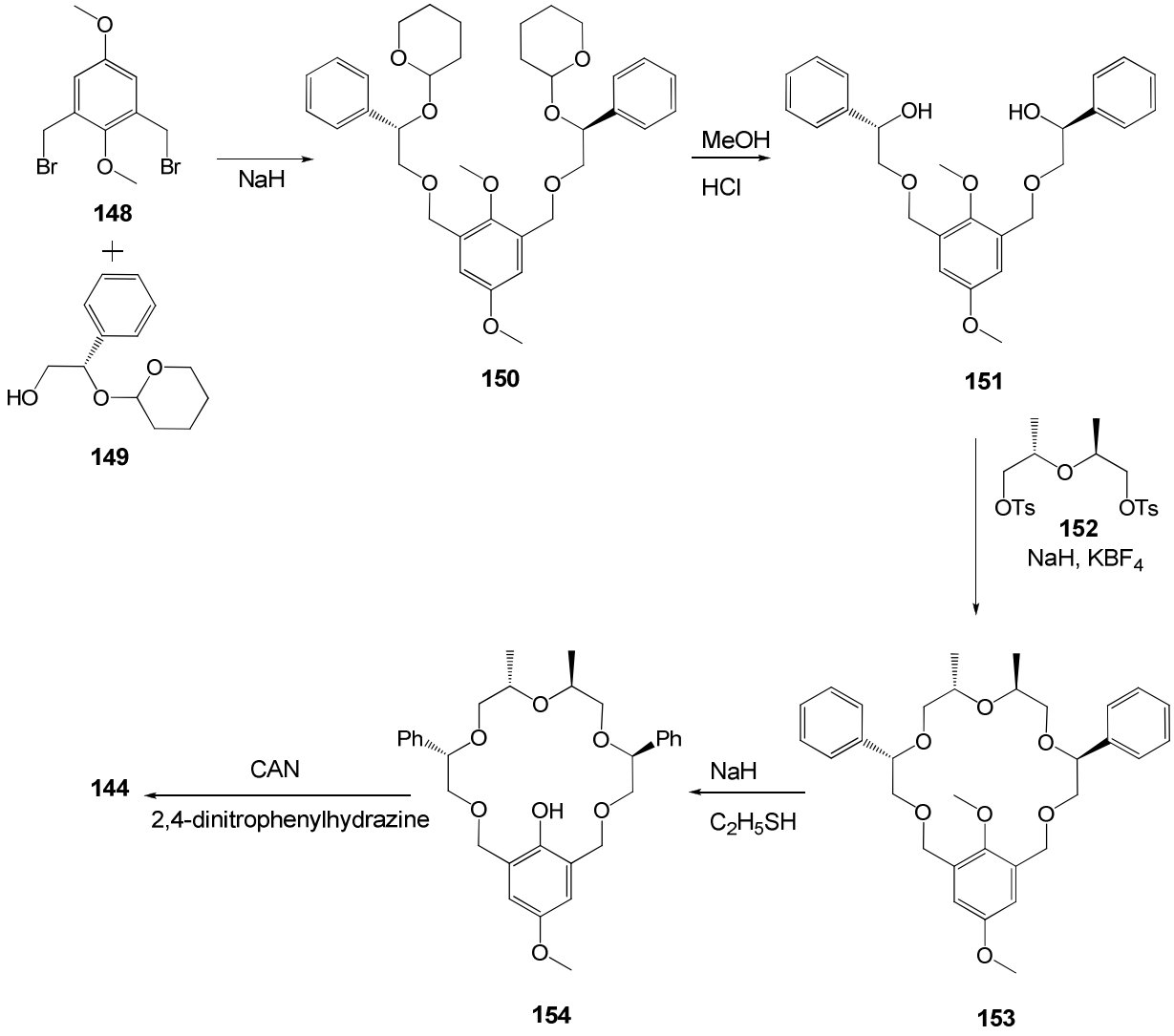


Figure 13: Crown Ethers **144**-**147**

Each of the macrocycles were synthesised using the same general procedures and the same elements, but by varying the order in which the steps in the general procedure were carried out and the elements added generated the different macrocycles. The components used in the synthesis were 2-phenyl-2-(tetrahydro-2H-pyran-2-yloxy)ethanol (both *R* and *S*) (**149**); (*S,S*)-2,4-dimethyl-3-oxapentane-1,5-ditosylate (**152**); 1,3-*bis*(bromomethyl)-2,5-dimethoxybenzene (**148**), and 2,4-dinitrophenylhydrazine. To synthesise **144** and **146**, 1,3-*bis*(bromomethyl)-2,5-dimethoxybenzene was reacted with **149** [(*S*) **149** for synthesis of **144** and (*R*) for **146**] using sodium hydride producing **150**. **150** was deprotected with methanol containing a

small amount of hydrochloric acid yielding **151**. The deprotected product, (*R* or *S*) **151**, was then reacted with (*S,S*)-2,4-dimethyl-3-oxapentane-1,5-ditosylate with sodium hydride and potassium borofluoride to create the enantiomers of **153**. Demethylation was carried out on the enantiomers of **153** using ethanethiol and sodium hydride in dimethylformamide producing the enantiomers of this **154**. **154** was then treated with cerium(IV)ammonium nitrate (CAN) followed by 2,4-dinitrophenylhydrazine to give target products **144** and **146**. The example synthetic pathway for **144** is shown in scheme 12.



Scheme 12: Synthesis of **144**

The difference in the synthesis of crown ethers **145** and **147** is that **152** was used in the first step and **148** was used in the closing of the macrocycle. Binding tests were carried out on these macrocycles with 1-amino-2-propanol, 2-amino-1-propanol, 2-amino-3-methyl-1-butanol and 2-amino-2-phenylehtanol. The results of these tests show that

macrocycles **144** and **146** show better enantiomeric selectivity than **145** and **147** for the series of aminoalcohols that were tested. Compound **144** was shown to have enantioselectivity for the *R* enantiomers of each of the aminoalcohols tests, with the most pronounced selectivity being seen for 2-amino-2-phenylehtanol with a log (Ka^R/Ka^S) value of 1.06. Compound **146** was shown to have enantioselectivity for the *S* enantiomers of each of the aminoalcohols tests, with the most pronounced selectivity observed for 2-amino-2-phenylehtanol with a log (Ka^S/Ka^R) value of 0.77.

Hayward *et al.* synthesised a number of chiral crown ethers, **155**, **156** and **157**, using (+)-(*1S,2S*)-*trans*-cyclohexane-1,2-diol.[33]

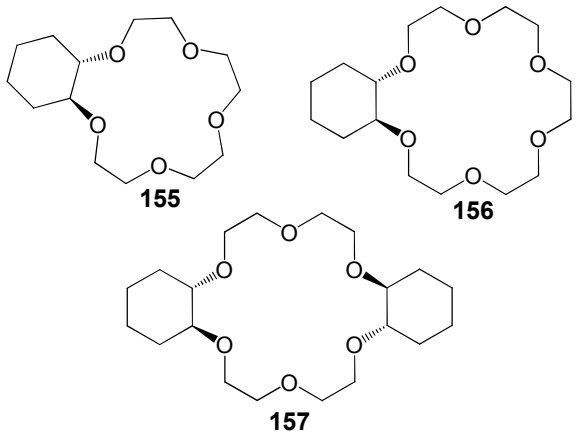
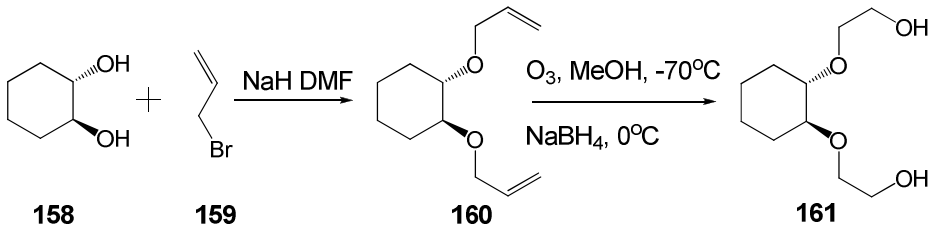


Figure 14: Crown ethers **155** *to***157**

The trans cyclohexane-1,2-diol (**158**, scheme 13) was reacted with allyl bromide (**159**). The product (**160**) was subjected to ozonolysis with a reductive work-up to produce the 'half-crown' diol (**161**).



Scheme 13: synthesis of **161**

161 was tosylated and the tosylated product was reacted with an equivalent of **161** to give the dicyclohexane 18-crown-6 ether product (**157**). **161** was reacted with 2,2'-oxy*bis*(ethyl tosylate) to give the 15-crown-5 ether (**155**) and with pentaethyleneglycol ditosylate to give the mono-cyclohexane 18-crown-6 ether product (**156**).

Vincent *et al.* reported the synthesis of eight chiral crown ethers containing *α,α*-trehalose, **162**-**169**.[34]

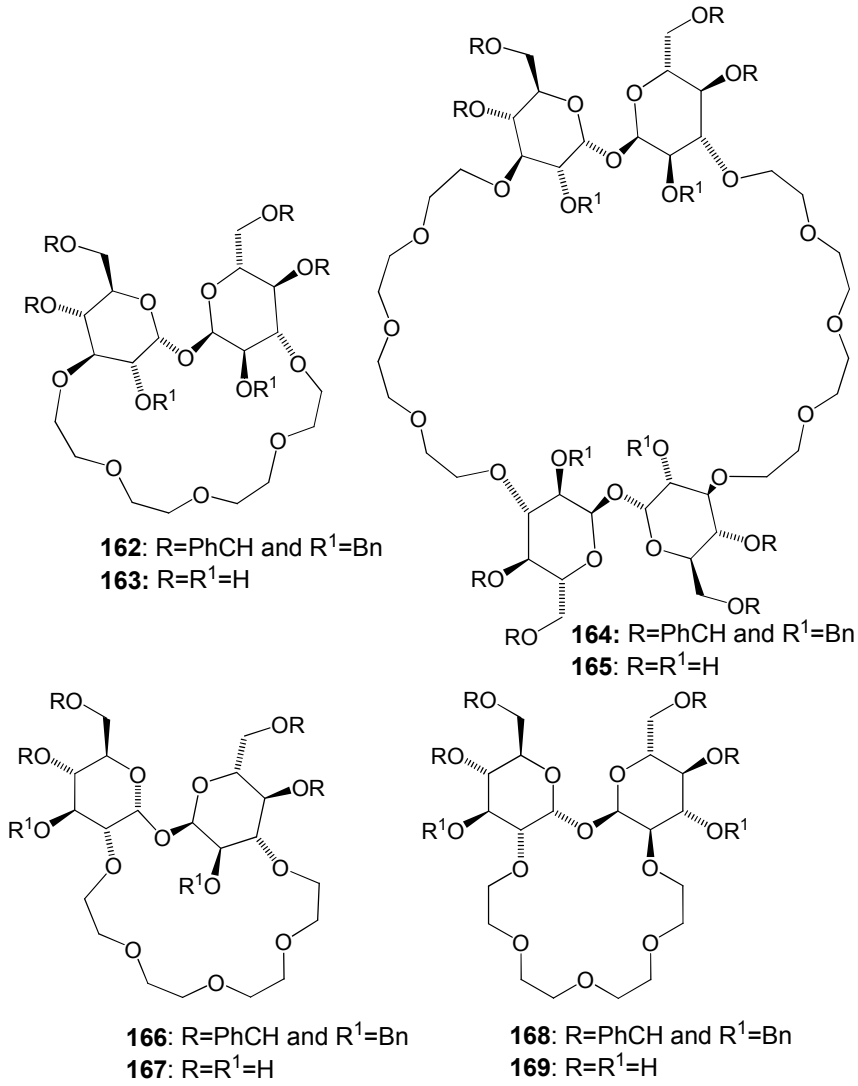
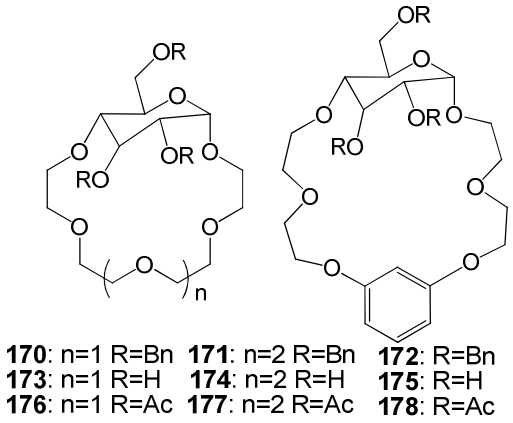


Figure 15: Crown ethers **162**-**169**

The crown ethers **162**, **164**, **166** and **168** were prepared via the reaction of the appropriately protected trehalose diol derivative with tetraethylene glycol ditosylate, giving the target products in yields ranging from 10 % to 70 %. The benzyl protecting groups were then removed by hydrogenation using palladium/carbon catalyst giving **163**, **165**, **167** and **169** in yields of 60 % to 94 % for the deprotection step.

A series of crown ethers have also been synthesised with *D*-glucose in the structure, **170**-**178**.[35]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gave crown ether **172**. Crown ethers **173**, **174** and **175** were prepared by the hydrogenation of the protected crown ethers (**170**, **171** and **172** respectively) over palladium/carbon catalyst. Crown ethers **176**, **177** and **178** were synthesised by the acetylation of the crown ethers **170**, **171** and **172** respectively. Crown ether **171** has been shown to have enantiomeric selective catalyst properties for the Michael addition reaction of methyl phenylacetate with methyl acrylate utilising potassium *tert*-butoxide as the base. With one equivalent of **171,** one equivalent potassium *tert*-butoxide, fifteen equivalents of methyl acrylate and forty equivalents of methyl phenylacetate the reaction resulted in 63 % e.e. (*S*) at -78 ^{o}C and 59 % e.e. (*S*) at -50 ^{o}C in toluene. But with one equivalent of **171** to five equivalents of potassium *tert*-butoxide with fifteen equivalents of methyl acrylate and twenty equivalents of methyl phenylacetate the reaction the reaction gave 47% e.e. (*R*) at 30^{o}C. The reasons for the variable preference of the one crown ether for both *R* and *S* configurations of dimethyl 2-phenylpentanedioate in this reaction with changing conditions is not understood.

Another series of chiral based crown ethers that also include carbohydrates as a source of the chirality have also been synthesised, **186**-**195**.[36,37] All these crown ethers have a hexaethyleneglycol, pentaethyleneglycol or tetraethyleneglycol chain attached to the carbohydrate derivative at both ends. They vary mainly in the location of the attachment to the carbohydrate and also in the carbohydrate derivative and are very similar in structure to crown ethers **170** and **171**.

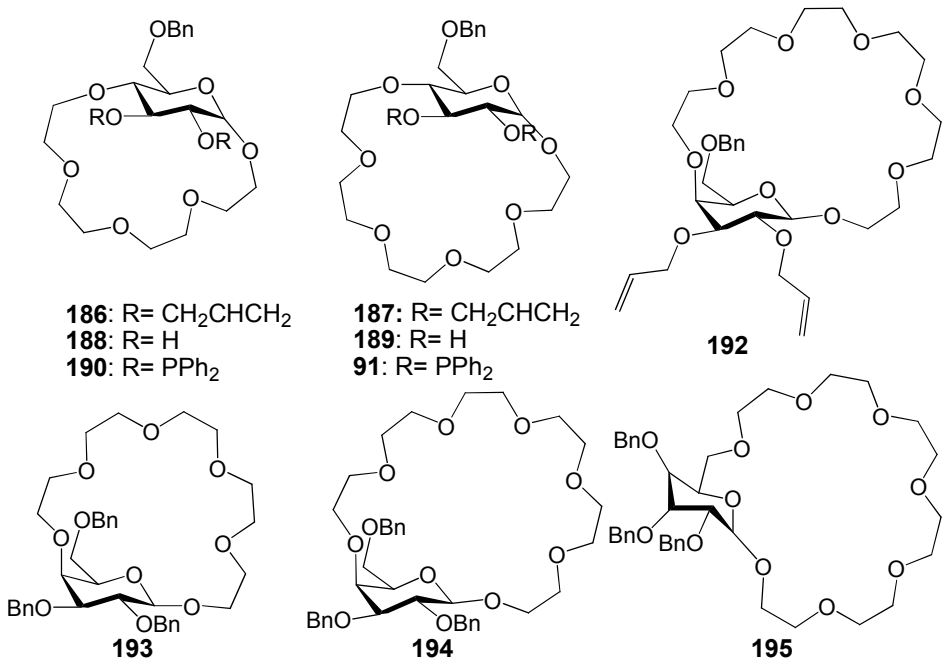


Figure17: Structures of crown ethers **186-195**

Although products **186**-**195** are quite similar to those in figure 15 the method of synthesis is different for this series than for **170**-**178**. The same general method is employed for each of these macrocycles (**186**-**195**). There are three different starting materials used, **196**, **197** and **198**.

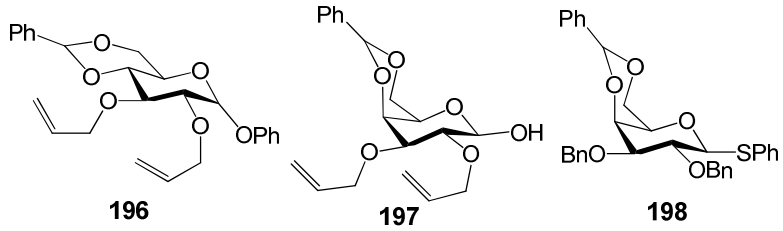


Figure 18: Structures of **196**, **197** *and* **198**.

Crown ethers **186**-**191** were synthesised from **196**, **192** was synthesised from **197** and **193**-**195** were synthesised from **198**. Each macrocycle was prepared using the same synthetic pathway. The 2-phenyl-1,3-dioxane group in each of the starting materials was reductively cleaved to give a benzyl protected alcohol and a free alcohol. This cleaved product was then etherified with *bis*(2-chloroethyl)ether to form ethylene glycol derivatives. For the synthesis of **195** the starting material (**198**) was reductively cleaved using lithium aluminium hydride and aluminium trichloride in dichloromethane and diethyl ether. The reductions of **196** and **197** were carried out using sodium cyanoborohydride in tetrahydrofuran followed by acidic work-up with hydrogen chloride in diethyl ether. The ethylene glycol derivatives were then alkoxylated with diethyleneglycol, triethyleneglycol or tetraethyleneglycol depending on the size of the ring being synthesised. The ring was closed via the elimination of phenol for **186**-**192** or elimination of benzenethiol for **193**-**194**. Crown ethers **188** and **189** were synthesised by deallylation of crown ethers **186** and **187** respectively. The reaction of **188** and **189** with chloro-diphenylphosphine with pyridine in tetrahydrofuran yielded **190** and **191**. **190** and **191** were then reacted with Rh(COD)acac, the acac group is replaced by the two phosphine groups that are a part of the crown ether. This was done to synthesise chiral catalysts. Initial testing with these catalysts showed positive results for the possible use of these crown ethers as chiral catalysts for hydrogenation reactions of 2-acyl-*N*-2-dehydroamino acid derivatives.

A series of chiral and *meso*-crown ethers have been synthesised using tetraoxaspiro(5,5)undecane and trioxa-azaspiro(5,5)undecane as the chiral subunit, **199** to **214**.[38] Synthesis was carried out by the treatment of the tetraoxaspiro(5,5)undecane

(for crown ethers **199**, **200**, **201**, **211** and **212**) or trioxa-azaspiro(5,5)undecane (for crown ethers **202**-**210**, **213** and **214**) with hydride and then the slow addition of the required tosylate. There were sixteen different macrocycles synthesised in this series, with yields varying from 2 % to 55 % depending not only on the macrocycle being synthesised but also the hydride used. The crown ethers in this series can be grouped into two main groups; [1+1] cyclocondensation products (**199-210)**, and [2+2] cyclocondensation products (**211**-**214**).

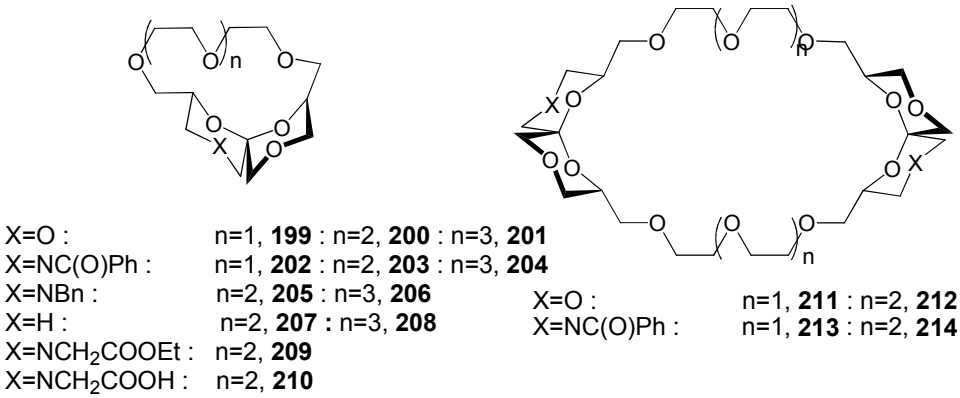


Figure 19: Crown ethers **199**-**214**

Crown ethers **211-214** were isolated in low yields, 2 % to 22 %, while **199-200** were isolated in higher yields, 6 % to 55 %. Crown ethers **202-204** were generated containing the structure trioxa-azaspiro(5,5)undecane. Compounds **203** and **204** were then reduced to give the benzylamine crown ethers **205** and **206** or reduced with a hindered hydride, lithium triethyl borohydride and then hydrolysed to give the free amine crown ethers **207** and **208**. Crown ether **207** was then alkylated with ethyl 2-bromoactate to yield **209** which was subjected to hydrolysis to give the free acid **210**.

Another series of chiral crown ethers have been synthesised using a spiro acetal subunit, 1,7-dioxaspiro(5,5)undecane ring system, as the chiral subunit, **215**-**220**.[39] The crown ethers in this series can be broken down into two main groups; those made with diaxial 1,7-dioxaspiro(5,5)undecane-3,5-diol, **215**-**217**, and those made with diequatorial 1,7-dioxaspiro(5,5)undecane-3,5-diol, **218**-**220**. The only variable within these groups is that of the size of the ring.

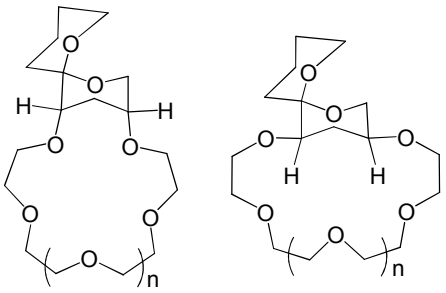


Figure 20: Structures **215**-**220**

The diaxial crown ethers, **215**-**217**, were synthesised by the addition of tetraethylene glycol ditosylate, pentaethylene glycol ditosylate or hexaethylene glycol ditosylate to diaxial 1,7-dioxaspiro(5,5)undecane-3,5-diol giving the three crown ethers with yields of 48 % (**215**), 42 % (**216**) and 32 % (**217**). The diequatorial crown ethers, **218**-**220**, were synthesised by the addition of tetraethylene glycol ditosylate, pentaethylene glycol ditosylate or hexaethylene glycol ditosylate to diequatorial 1,7-dioxaspiro(5,5)undecane-3,5-diol resulting in yields of 34 % (**218**), 28 % (**219**) and 42 % (**220**). The axial analogues exhibit more than 1000 fold better complexing ability to sodium and potassium than the equatorial analogues. Compounds **215** and **216** with n=1 and n=2 exhibit a higher binding affinity for potassium than 18-crown-6, with Log Ka values of 1.29 and 1.21 respectively compared to 0.83 for 18-crown-6. Although these macrocycles are chiral and were enantiomerically pure, no testing of chiral recognition was reported.

Luk'yanenko *et al.* synthesised a series of chiral crown ethers using *L*-tartaric acid derivatives as chiral subunits, **221-232**.[40] Yields for this series ranged from 6 % to 45 %. There were two main groups within the series, [1+1] (**221-226**) and [2+2] (**227-232**) products.

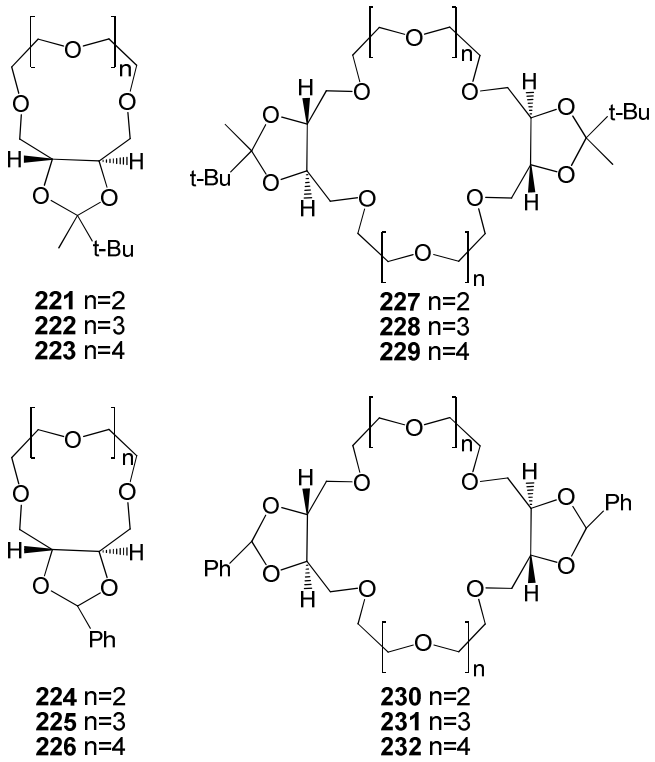
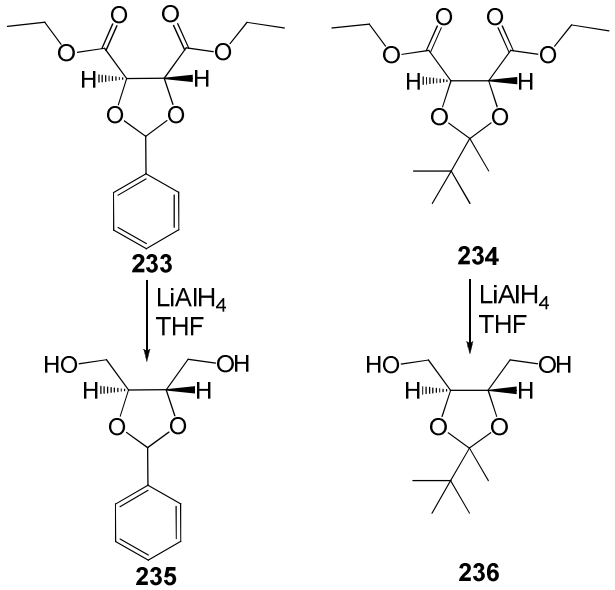


Figure 21: Structure of crown ethers **221**-**232**

The synthesis of macrocycles **221**-**232** began with the protection of the alcohols in diethyl *L*-tartrate with benzaldehyde or pinacolone to give **233** and **234** (scheme 15) respectively. Reduction of **233** and **234** with lithium aluminium hydride furnished the diols **235** and **236**.

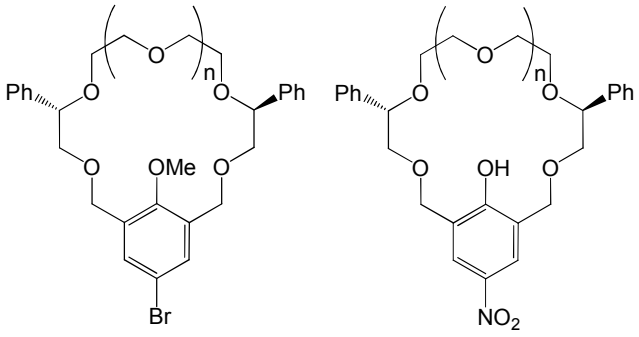


Scheme 15: Synthesis of **235** *and* **236**

The reaction of diols **235** and **236** with the appropriate polyethylene glycol ditosylate in the presence of sodium hydride and in dioxane gave the crown ether products. **221**-

223 and **227**-**229** were synthesised using **236**. **224**-**226** and **230**-**232** were synthesised using **235**. The analogous [1+1] and [2+2] crown ethers were isolated from the same reaction, e.g. **221** and **223** were synthesised in the same reaction and separated after. The enantioselectivity of these crown ethers with *L*- and *D*-valine methyl ester hydrochlorides were evaluated. The crown ethers that displayed the highest enantioselectivity were **223**, **226** and **230**. The most noteworthy characteristic of these macrocycles is that if only the ring size is considered when looking at enantioselectivity it shows that with increasing ring size there is an inversion of enantioselectivity. The reason for this is not fully understood but is likely to do with the differing structure and stoichiometry of the host-guest complex as ring size changes.

A number of phenolic chiral crown ethers have been synthesised using (*S*)-(+)-mandelic acid derivatives.[41] There were twelve of these macrocycles synthesised (**237**-**248**) with four different substituents on the crown ether ring.



237 n=1
238 n=3
239 n=4

240 n=1
241 n=3
242 n=4

243 n=1
244 n=3
245 n=4

246 n=1
247 n=3
248 n=4

Figure 22: Compounds **237-248**

Crown ethers **237**-**239** were synthesised from the same starting materials varying the poly(ethylene glycol) ditosylate for the different ring sizes. Compounds **237**-**239** were synthesised first then modified to produce the other crown ethers. The synthesis was done in six steps from starting material to the *p*-nitro phenolic crown ethers, **240**-**242**.

The mandelic acid derivative, mono THP protected 1-phenylethane-1,2-diol, was reacted with 5-bromo-1,3-*bis*(bromomethyl)-2-methoxybenzene. The tetrahydropyran was removed to leave the diol. Cyclisation with the appropriate poly(ethylene) glycol ditosylate followed by the reaction with diethylene glycol ditosylate gave **237** in overall yield of 42 %. Reaction with triethylene glycol ditosylate gave **238** in overall yield of 34 %. Reaction with tetraethylene glycol ditosylate gave **239** in overall yield of 24 %. Debromination was carried out with *n*-BuLi and water work-up to give the methoxy crown ether in overall yields of 25 % for **243**, 21 % for **244** and 16 % for **245**. Demethylation with sodium ethanethiolate gave the phenolic crown ether product in overall yields of 23 % for **246**, 18 % for **247** and 4.8 % for **248**. Macrocycles **246**, **247** and **248** were nitrated to give the *p*-nitro phenolic crown ethers in overall yields of 13 % for **240**, 6.2 % for **241** and 2.0 % for **242**. The *p*-nitro phenolic crown ethers were tested for chiral recognition of secondary amines. Compound **241** showed best selectivity, with **240** being too small to accommodate a secondary amine and **242** being too large to efficiently inhibit the binding of the unwanted enantiomer.

Karakaplan *et al.* synthesised a series of chiral crown ethers containing a (*p*-methoxyphenoxy)methyl moiety, **249**-**253**.[42]

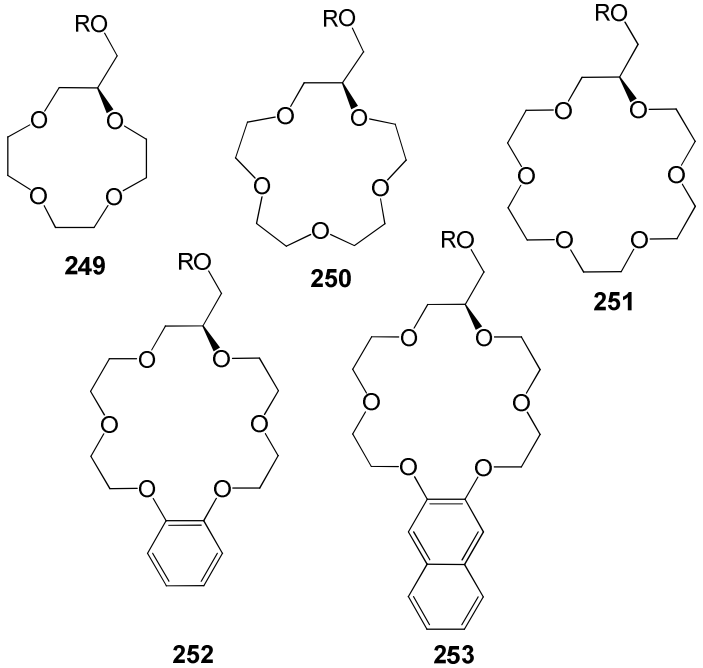
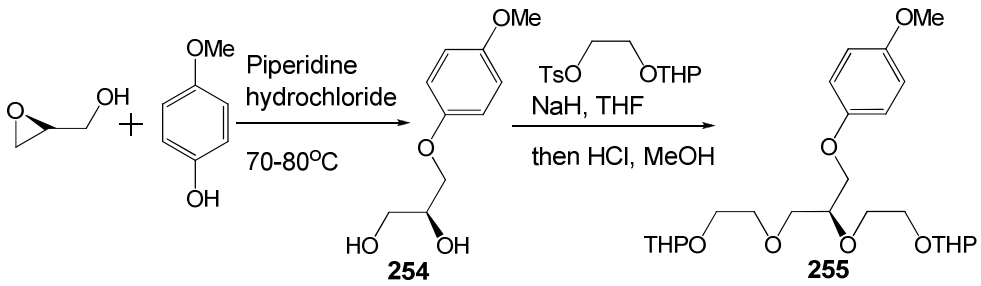


Figure 23: Crown ethers **249**-**253**

The chiral subunit, **254**, was synthesised by the reaction of (*S*)-glycidol and *p*-methoxyphenol with piperidine hydrochloride as catalyst.

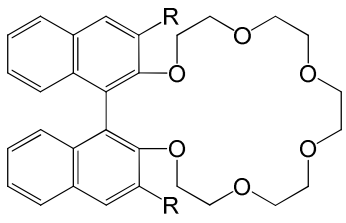


Scheme 16: Synthesis of **255**

254 was used directly with triethylene glycol ditosylate to synthesise crown ether **249** in 15 % yield and tetraethylene glycol ditosylate to synthesise crown ether **250** in 39 % yield. **254** was also used to synthesise the chiral precursor to the 18-crown-6 ethers (**251**, **252** and **253**). **254** was reacted with 1-(tetrahydropyranyloxy)-2-[(*p*-tolylsulfonyl)oxy]ethane to give the chiral triethylene glycol derivative, **255**, which was deprotected followed by reaction with triethylene glycol ditosylate to give **251** in 18 % yield. To synthesise crown ethers **252** and **253** the correct subunits had to be synthesised. The benzo-subunit was produced via the tosylation of 1,2-*bis*-(2-hydroxyethoxy)benzene and the product of this reaction was then reacted with chiral triethylene glycol derivative to give the crown ether **252** in 12 % yield. The naphtho subunit was synthesised by the reaction of 2,3-dihydroxynaphthalene and ethylene oxide. The product of this reaction was tosylated followed by reaction with the chiral triethylene glycol derivative to give **253** in 12 % yield. **250**-**253** were then tested for binding and enantioselectivity, by UV spectroscopy titration, towards two amino acid ester hydrochloride salts, alanine methyl ester hydrochloride and phenylalanine methyl ester hydrochloride. Compound **250** exhibited the strongest binding and best enantioselectivity towards alanine methyl ester hydrochloride with a Log (K_a^L/K_a^D) value of 0.76, while it showed no enantioselectivity towards phenylalanine methyl ester hydrochloride. Compound **253** exhibited the strongest binding and best enantioselectivity towards phenylalanine methyl ester hydrochloride with log (K_a^D/K_a^L) value of 0.38 with poor recognition of alanine methyl ester hydrochloride. Both **251** and **252** did not exhibit enantioselectivity for either of the amino acid ester hydrochloride salts tested.

Lingenfelter *et al.* reported the synthesis of a series of chiral 20-crown-6 ethers using binaphthyl derivatives as chiral subunits.[43] The general structure for these chiral crown ethers is shown in figure 24 below, both (*R*) and (*S*) enantiomers were synthesised and

the only differences between the structures is the substituents on the binaphthyl derivatives.

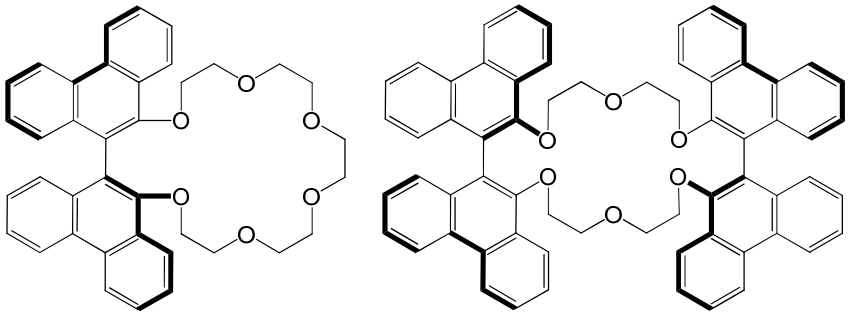


256 R=H
257 R=Me
258 R=CH_2OMe
259 R=CH_2OPh
260 R=CH_2O-p-$C_6H_4OCH_3$
261 R=CH_2SPh
262 R=CH_2SCH_2Ph
263 R=C_2ON_2Ph (2-phenyl-1,3,4-oxadiazole)
264 R=Ph
265 R=$C_6(Me)_5$

Figure 24: Structure of crown ethers **256**-**265**

The synthesis of the crown ether was done by the addition of pentaethylene glycol ditosylate to 2,2'-dihydroxy-1,1'-binaphthyl for crown ether 2**56**, with, 3,3'-dimethly-2,2'-dihydroxy-1,1'-binaphthyl for crown ether **257** and with 3,3'-dimethoxymethyl-2,2'-dihydroxy-1,1'-binaphthyl for crown ether **258**. The methoxy of the methoxymethyl group in **258** was then substituted with phenoxy to produce **259**, with *p*-methoxyphenoxy to produce **260**, with phenylsulfane to produce **261** and with benzylsulfane to produce **262**. The methoxy of the methoxymethyl group in **258** was also converted into a cyano group from which the 2-phenyl-1,3,4-oxadiazole, **263**, was synthesised and then the 2-phenyl-1,3,4-oxadiazole could be replaced with a phenyl group to produce **264** and with pentamethylphenyl to produce **265**. **256**-**265** were then tested for chiral recognition towards two guests, phenylalanine methyl ester perchlorate salt and valine methyl ester perchlorate salt. **264** has the highest chiral recognition towards the guests tested, with substantially higher recognition towards the phenylalanine methyl ester perchlorate salt with an enantiomer distribution constant (EDC) of 19.5 with *D*-phenylalanine methyl ester perchlorate salt being the preferred guest. **256** showed the least chiral recognition towards the valine methyl ester perchlorate salt with an EDC of 1.1 and was only slightly better for the chiral recognition of the phenylalanine methyl ester perchlorate salt with an EDC of 1.6.

Two chiral crown ethers have been synthesised with a biphenanthryl subunit containing the chiral centre, **266** and **267**.[44]

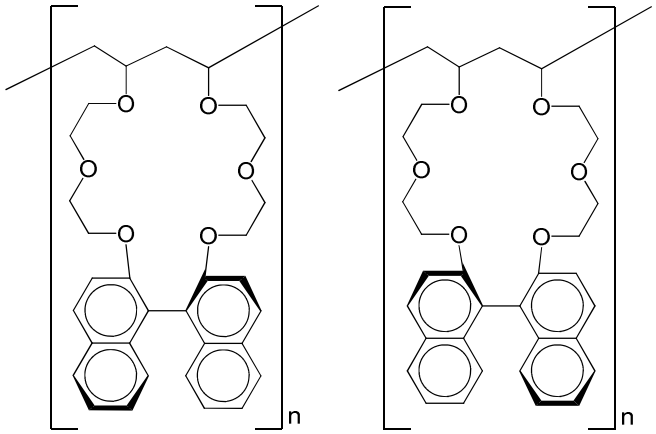


266 **267**

Figure 25: Structures of **266** *and* **267**

266 and **267** were synthesised in 4 steps, the first three steps identical for both macrocycles. The synthesis started with the oxidation of 9-phenanthrylmagnesium bromide with *t*-butyl perbenzoate and the hydrolysis of the *t*-butyl ester to give 9-phenanthrol. Oxidative coupling on the 9-phenanthrol to make 10,10'-dihydroxy-9,9'-biphenanthryl, produced a racemic mixture, which was then purified into the pure (*R*) and (*S*) enantiomers. The (*S*) enantiomer underwent a condensation reaction with pentaethyleneglycol ditosylate to give **266** in 22 % overall yield. The (*R*) enantiomer was reacted with diethyleneglycol ditosylate to give **267** in 12.5 % overall yield. **266** and **267** were then tested for chiral recognition with three chiral guest molecules, methyl (±)-phenylglycinate, (±)-1-phenylethylamine hydrochloride and (±)-1,2-diphenylethylamine hydrochloride. **266** was shown to have better enantiomeric selectivity for each guest species tested.

Chiral polymeric crown ethers, (*R*) and (*S*) enantiomers of a chiral 21-crown-6 ether, have been synthesised containing binaphthyl subunits, **268** and **269**.[45]



268 (*S*) **269** (*R*)

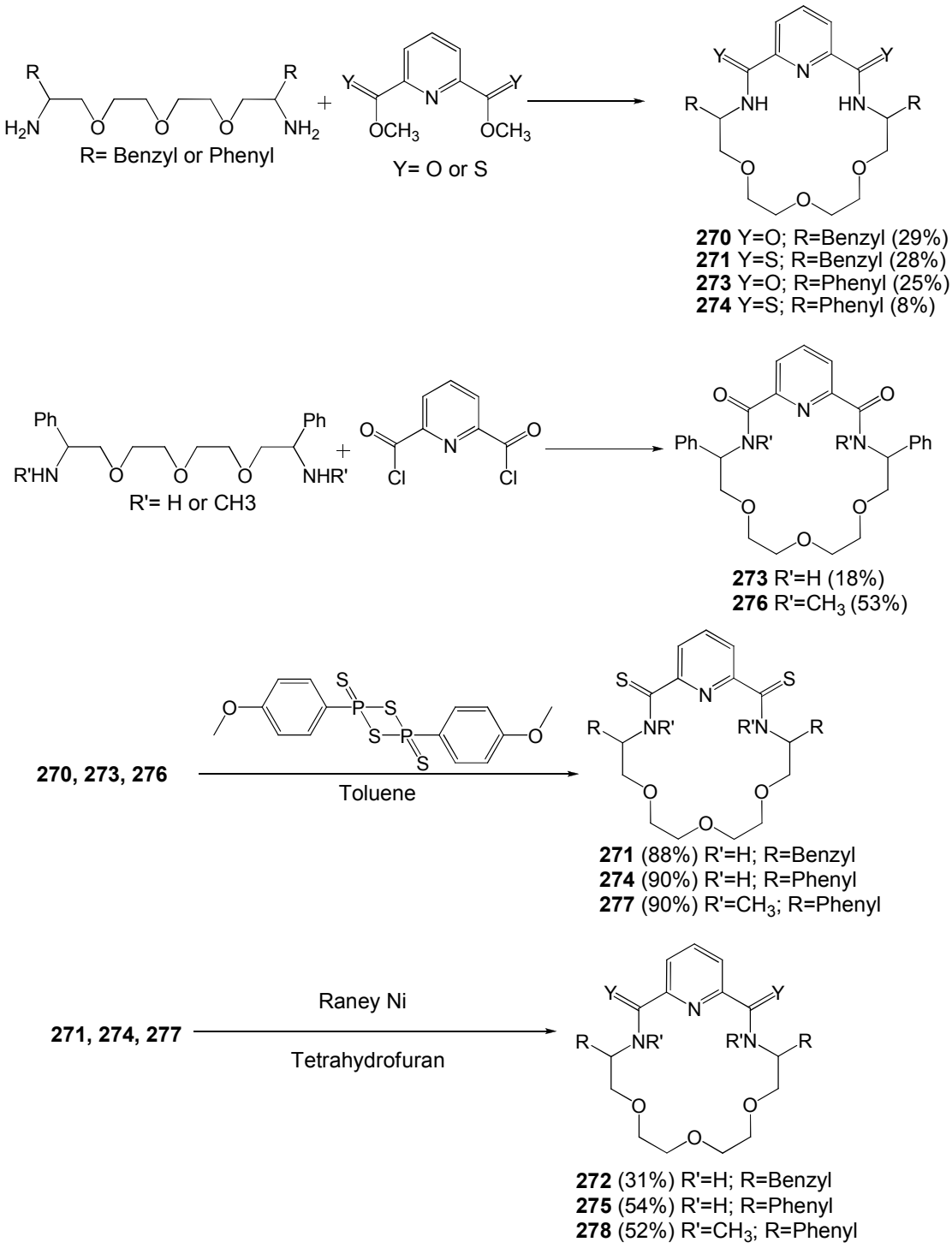
Figure 26: Structures of **268** *and* **269**

The synthesis of the polymer crown ether products was done by cationic catalysis, of (*S*) or (*R*) 2,2'-*bis*[2-(2-vinylethoxy)ethoxy-1,1'-binaphthyl. Different catalysts and

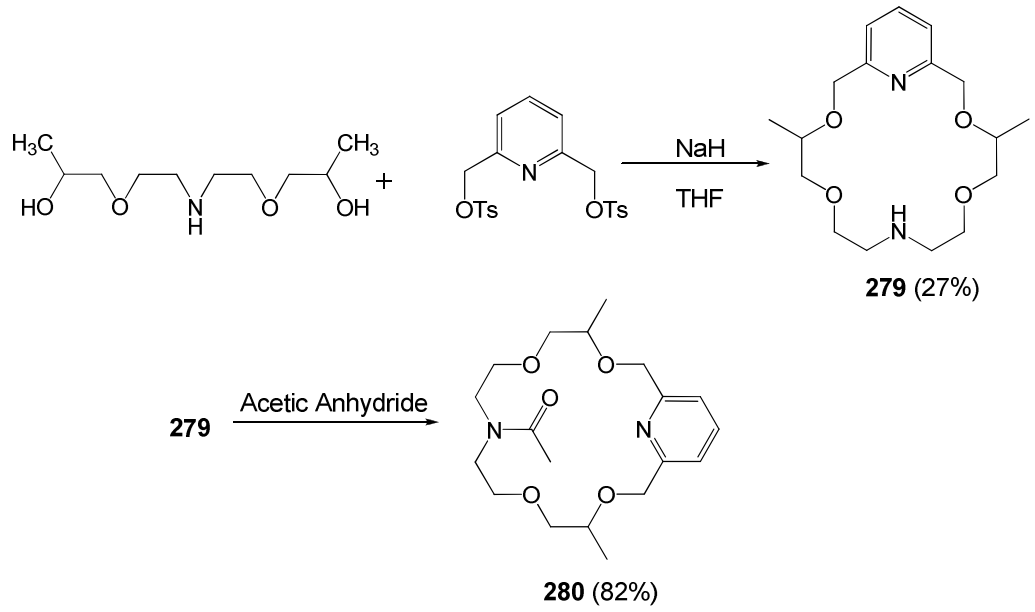
solvent combinations were used to try to optimise the yield of the polymer. The yields obtained for the (*S*) polymer range from 23.7 % to 40 % and for the (*R*) polymer range from 35.9 % to 89.4 %. The use of boron trifluoride etherate as the catalyst in nitroethane gave the highest yields for both enantiomers. The (*S*) or (*R*) polymeric crown ethers gave values of optical rotation that are very similar but in opposite directions. The (*R*) polymer exhibits chiral recognition close to that of the non-polymeric (*R*) binaphthyl 20-crown-6 reported by Cram *et al.*[43]

1.1.4 Chiral Aza-Crown Ethers

A series of eleven chiral pyridine-18-crown-6 ethers have been synthesised, **270**-**280**, with all macrocycles reported being the (*S,S*) isomer.[46] The general structure of **270-278** is the same, differing only in the substituents on the crown ether ring. **279** and **280** have the same general structure as each other and are different from the other nine macrocycles in the series. **270**, **273** and **276** were synthesised first and then modified to yield **271**, **272**, **274**, **275**, **277** and **278**. This was done by the method shown in scheme 17 below. Aza-crowns **279** and **280** were synthesised by the method shown in scheme 18.



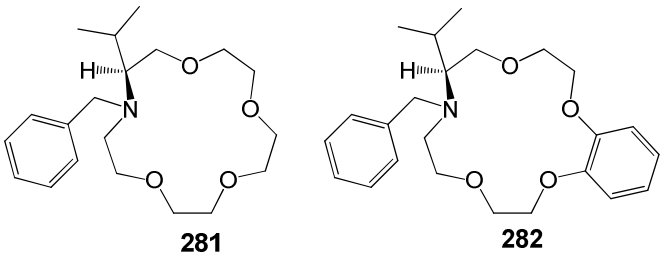
Scheme 17: Synthesis **270**-**278**



Scheme 18: Synthesis **279**-**280**

Binding studies were carried out by NMR with [*α*-(1-naphthyl)ethyl]ammonium perchlorate and **270**, **273**, **274**, **276**, **277** and **278**. Log K values of **270** were measured with [*α*-(1-naphthyl)ethyl]ammonium perchlorate in 50/50 deuterated chloroform/deuterated methanol and Log K values were too low to measure accurately and in deuterated nitromethane the Log (K^R/K^S) was found to be 0.2. Log K values of **273** were measured with [*α*-(1-naphthyl)ethyl]ammonium perchlorate in 50/50 deuterated chloroform/deuterated methanol and Log K^R was found to be 0.7 and Log K^S was too low to measure accurately. Log K values of **274** were measured with [*α*-(1-naphthyl)ethyl]ammonium perchlorate in 50/50 deuterated chloroform/deuterated methanol and Log (K^R/K^S) was found to be 0.37. Log K values of **276** were measured with [*α*-(1-naphthyl)ethyl]ammonium perchlorate in 50/50 deuterated chloroform/deuterated methanol the Log K values were too low to measure accurately and in deuterated nitromethane Log (K^R/K^S) was found to be 0.2. Log K values of **277** were measured with [*α*-(1-naphthyl)ethyl]ammonium perchlorate in 50/50 deuterated chloroform/deuterated methanol and Log (K^R/K^S) was found to be 0.2. Log K values of **278** were measured with [*α*-(1-naphthyl)ethyl]ammonium perchlorate in 50/50 deuterated chloroform/deuterated methanol and Log (K^S/K^R) was found to be 0.1 and in deuterated nitromethane the Log K values were too high to measure accurately.

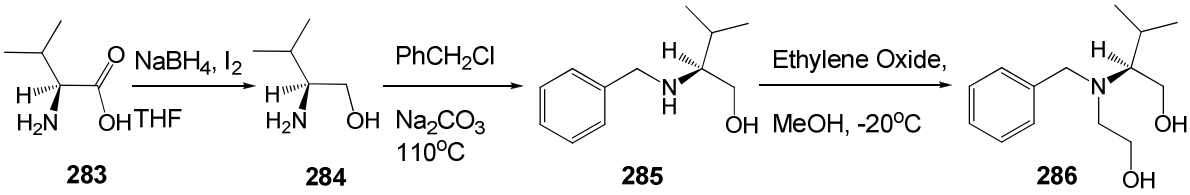
Two chiral monoaza-15-crown-5 ethers have been synthesised from *L*-valinol, **281** and **282**.[47,48]



281 **282**

Figure 27: Aza-crown ethers **281** *and* **282**

281 and **282** were synthesised in four steps, starting with the reduction of *L*-valine, **283**, to *L*-valinol, **284**. Valinol was then benzylated to form the *N*-benzyl amino alcohol, **285**. This product was then reacted with ethylene oxide to give the diol, **286**, which could be used in the final step of the synthesis of the monoaza-15-crown-5 ethers.

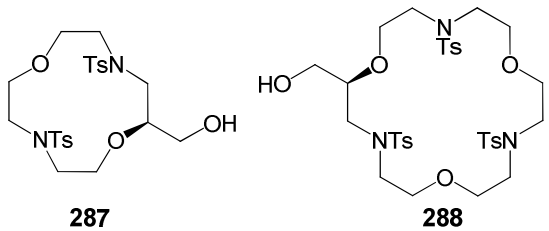


283 **284** **285** **286**

Scheme 19: Synthesis of **286**

286 was then employed in a condensation with triethylene glycol ditosylate to synthesise aza-crown ether **281** or 1,2-*bis*(2-tosylethoxy)benzene to synthesise aza-crown ether **282**. Binding studies were carried out with phenylmethylammonium perchlorate and naphthylmethylammoniun perchlorate. The data showed that both **281** and **282** display enantiomeric recognition of phenylethylammonium perchlorate with log (K_a^R/K_a^S) values of 0.50 and 0.26 respectively and naphthylmethylammoniun perchlorate with log (K_a^S/K_a^R) values of 1.5 and 1.0 respectively.

One triaza-18-crown-6 ether, **288**, and one diaza-12-crown-4 ether, **287**, have been synthesised by Lee *et al*.[49]

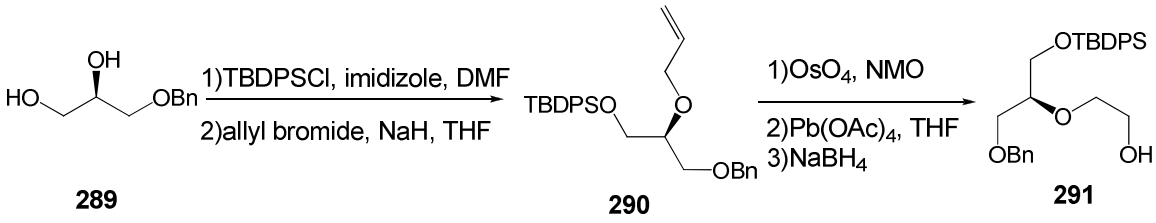


287 **288**

Figure 28: Aza-Crown ethers **287** *and* **288**

288, was synthesised in 11 steps, starting with (*R*)-1-benzylglycerol, **289.** The primary hydroxy group was selectively protected with TBDPS. Allylation was carried out on the secondary alcohol to give **290**. The allyl group in **290** was converted into a hydroxyethyl group in two stages. Firstly dehydroxylation of the allyl group utilising

osmium oxide, followed by diol cleavage using lead acetate and reductive work-up using sodium borohydride, to give **291**.

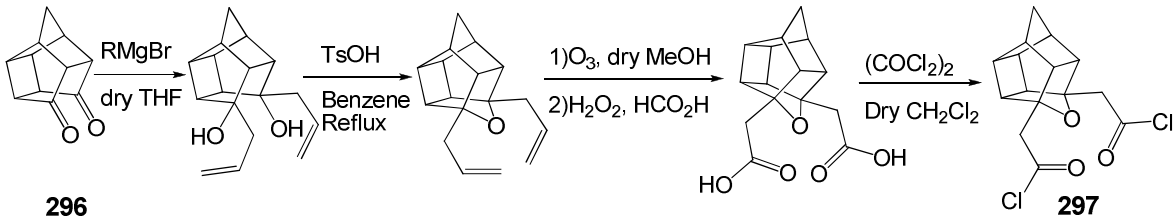


289 **290** **291**

Scheme 20: Synthesis of **291**

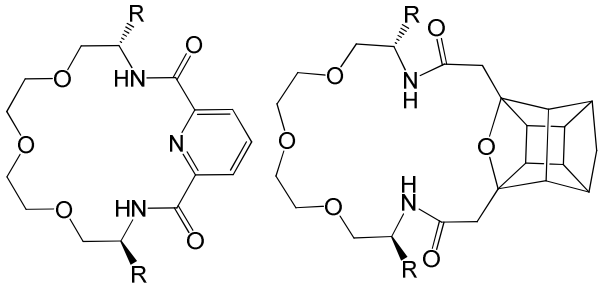
The alcohol group on **291** was tosylated and then reacted with 2-(2-tosylaminoethoxy)ethanol. Debenzylation followed by mesylation of the alcohol groups and reacting with 2-(2-(tosylamino)ethoxy)-*N*-tosylethanamine gave the TBDPS protected 18-crown-6. Deprotection with tetrabutylammoniun fluoride gave **288** in 14 % yield. For the synthesis of the diaza-12-crown-4 ether, **291** was debenzylated and the diol was tosylated. This ditosylate was then reacted with 2-(2-(tosylamino)ethoxy)-*N*-tosylethanamine to give **287** in 37 % yield.

Cage-annulated chiral aza-crown ethers, **292**-**295**, have been successfully synthesised utilising the reaction of the chiral diamines with diacid chlorides.[50] Of the two diacid chlorides used one was commercially available, 2,6-pyridinedicarbonyl dichloride, and the other had to be synthesised. The synthesis of the acid chloride was carried out in four steps (scheme 21) from the starting material pentacyclo [5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8,11-dione, **296**. **296** was first allylated with ally magnesium bromide, then dehydrated using *p*-toluene sulphonic acid. Ozonolysis in dry methanol was then carried out on the product of the dehydration reaction, followed by oxidative work-up, with hydrogen peroxide in methanoic acid to give the diacid, 5,5-Dicarboxymethyl-4-oxahexacyclo[5.4.1.$0^{2,6}$.$0^{5,10}$.$0^{5,9}$.$0^{8,11}$]dodecane. Treatment of the diacid with oxalyl chloride resulted in the diacid chloride product, **297**.



296 **297**

Scheme 21: Synthesis of **297**

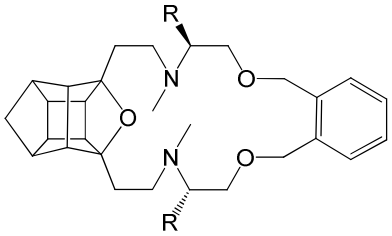


292 R=Ph
293 R=$CH(CH_3)_2$
294 R=Ph
295 R=$CH(CH_3)_2$

Figure 29: Crown ethers **292-295**

Cyclisation was carried out at high dilution (2.28 mM) with the appropriate chiral diamine and yields of the products varied from 25 % to 43 %. The enantioselectivity of these macrocycles was tested by U-tube transport studies with monitoring by optical rotation. The guest molecule for these studies was phenylglycine methyl ester hydrochloride. Results from this testing show high rate of transport (12 % h^{-1}) but with poor enantioselectivity.

Another series of chiral aza-crown ethers using pentacyclo-undecane-8,11-dione were synthesised, **298**-**300**.[51] The main difference in the structure of crown ethers **294**-**298** is an amine in **298**-**300** and an amide in **294** and **295**.



298 (*S*,*S*) R=$CH(CH_3)_2$
299 (*S*,*S*) R=$CH_2CH(CH_3)_2$
300 (*S*,*S*) R=C_6H_5

Figure 30: Structures of crown ethers **298**-**300**

298-**300** were synthesised with **297** and with 2-substitued-2-(methylamino)ethanol. The substituents on the 2-substitued-2-(methylamino)ethanol became the R groups on the macrocycles shown in figure 30. The product of this reaction was then reacted with *α,α*-dibromo-*o*-xylene to give the aza-crown ether product in yields of 17 % for **298**, 42 % for **299** and 35 % for **300**. Crown ethers **298** and **299** were shown to act as catalysts for the Michael addition reaction of 2-nitropropane to chalcone, giving low yield but an enantiomeric excess of up to 92 %.

A number of enantiomerically pure chiral phenazino-crown ethers have been synthesised, **301**-**309**.[52]

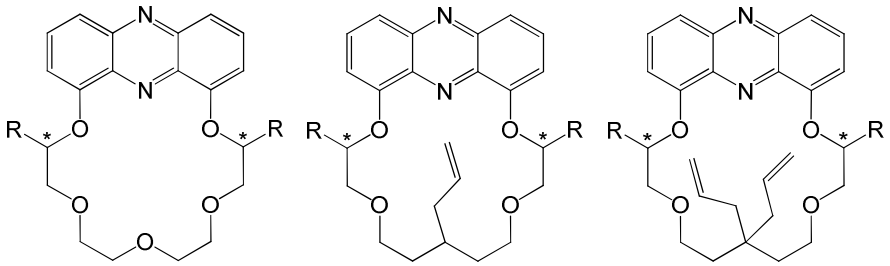


Figure 31: Aza-crown ethers **301**-**309**

Each of the (*R,R*) crown ethers and crown ether **304** (*S,S*) (figure 31), were synthesised from phenazine-1,9-diol with the appropriate ditosylate, with yields ranging from 12 % to 58 %. The other (*S,S*) crown ethers were synthesised from 1,9-dichlorophenazine and the appropriate diols with yields ranging from 14 % to 22 %. From tests carried out it was shown that all the (*R,R*) phenazino-crown ethers act as better chiral selectors than pyridino-18-crown-6 ethers for the perchlorate salts of PEA and NEA.

A series of chiral diaza-crown ethers (**310**-**317**) were synthesised[53] using enantiomerically pure *trans*-1,2-diaminocyclohexane.

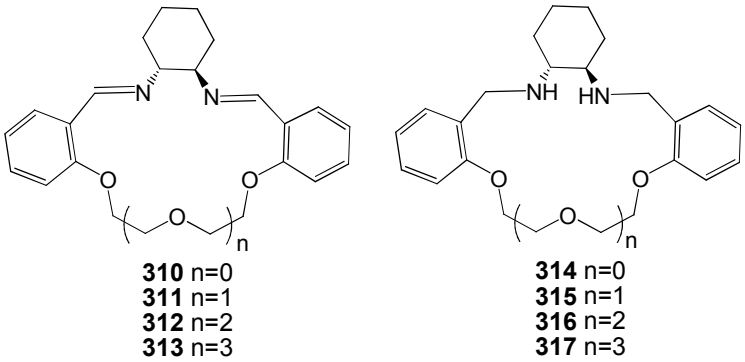
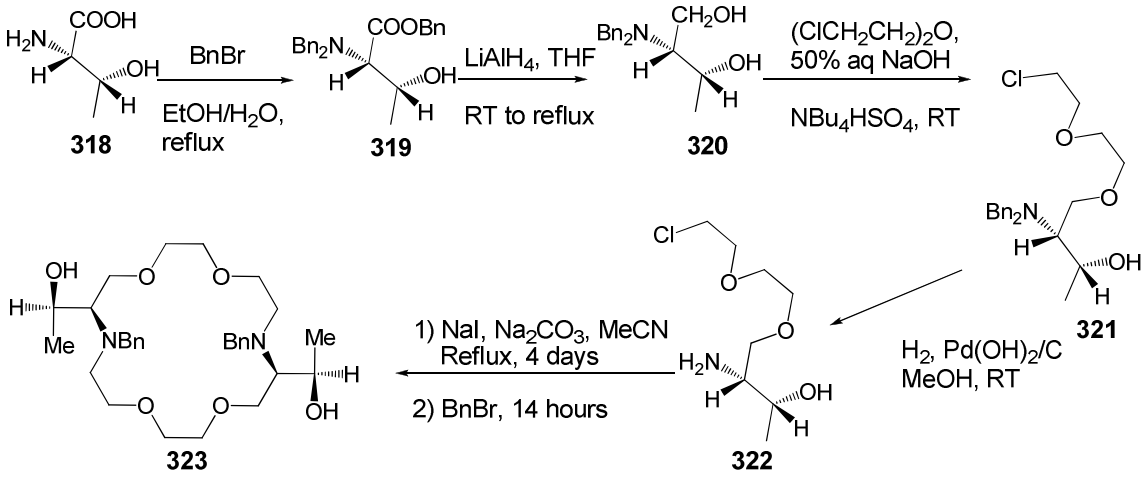


Figure 32: Aza-crown ethers **310**-**317**

310-**317** were synthesised by the reaction of *R,R*-trans-1,2-diaminocyclohexane with the correct ether linked dialdehyde, which ether linked dialdehyde used depends on the value of n. Crown ethers **310** and **311** were synthesised without solvent and gave yields of 89 % and 95 % respectively. Crown ethers **312** and **313** were synthesised in solution and both gave yields of 95 %. Crown ethers **310**-**313** were reduced to give crown ethers **314**-**317** in yields of 80 % for **314**, 91 % for **315**, 92 % for **316** and 91 % for **317**.

Chiral diaza-crown ether, **323,** has been made from *L*-threonine, **318**.[54]



Scheme 22: Synthesis of diaza-crown ether **323**

This was a six step synthesis with 22 % total yield. The first step was benzylation of *L*-threonine, **318**, producing **319**, which was reduced with lithium aluminium hydride to yield the diol **320**. **320** was reacted with diethylene glycol dichloride, which reacted solely with the primary alcohol to give **321**. **321** underwent deprotection with Pearlman's catalyst resulting in amine **322**. **322** was treated with sodium iodide, sodium carbonate under reflux in acetonitrile followed by addition of benzyl bromide to yield the macrocycle **323**. No testing of the binding abilities of **323** was reported.

1.2 P-glycoprotein Inhibitors

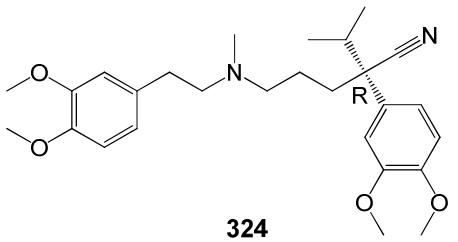
As part of the work of this project several compounds were tested as P-gp inhibitors. The positive results obtained from the initial testing incited some development work. This investigation lead to compounds which displayed improved activity as P-gp inhibitors. This work will be detailed in chapter five, but featured here is the introduction into the concept of P-gp inhibition.

P-glycoprotein (P-gp) is a multidrug efflux pump; it is one of the membrane bound glycoproteins that can cause multidrug resistance (MDR). P-gp keeps a wide variety of foreign substances, e.g. toxic agents and drugs, from being absorbed. P-gp plays an important role in the cell but they have been known to over express in cancer cells and as such decrease the concentration of chemotherapeutics in these cells, which in turn allows the cancer cells to survive. P-gp inhibitors are of increasing interest because

they potentially have multiple drug resistance reversing activity, by inhibiting the action of P-gp, and also can be made to have little or no biological impact on healthy cells. This can have implications for the treatment of diseases such as cancer and HIV, as P-gp is able to confer resistance by detecting binding and moving a wide variety of hydrophobic and amphipathic compounds, including many anticancer drugs and HIV-protease inhibitors from inside to the outside of the cell.[55] P-gp inhibitors are also known as chemosensitizers and P-gp modulators. P-gp inhibitors can be grouped into seven classes based on their structural features. These classes are calcium channel blockers, calmodulin antagonists, protein kinase C inhibitors (PKCIs), natural products such as steroids, cyclic peptides, flavanoids and miscellaneous compounds. Miscellaneous compounds are the P-gp inhibitors that don't fit into any of the other classes. P-gp inhibitors can also be broadly separated into three categories based on their interaction with P-gp: high-affinity substrates of the pump; efficient inhibitors of ATP hydrolysis coupled P-gp transport and; partial substrates/inhibitors. Most chemosensitizers display their MDR reversal activities by competitively binding to the drug binding sites on P-gp or non-competitively binding to the modulatory site.

Studies have indicated that a chemosensitizer with potential for clinical use should meet the following requirements: the compound should have a minimum log P value of 2.92; the compound should have a main chain length of not less than 18 atoms; should have a high E_{HOMO} value; and should have a minimum of one tertiary nitrogen.[55] Although some compounds without a tertiary nitrogen atom do act as P-gp inhibitors, it is thought that the tertiary nitrogen is indispensable for the compound to be a highly efficient p-pg inhibitor.

(*R*)-Verapamil, **324**, is regarded as the standard P-gp inhibitor to which the mechanism and potency of all subsequently discovered P-gp inhibitors are compared to. (*R*)-Verapamil both inhibits P-gp if actively pumping and stimulates P-gp if it is inactive [56].



324

Figure 33: (R)-Verapamil

(*R*)-Verapamil is a sodium and calcium channel blocker. It binds reversibly to P-gp and inhibits the binding of many chemotherapeutic agents and other inhibitors of P-gp.

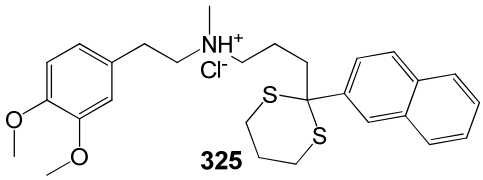


Figure 34: Ro11-2933

(*R)*-Verapamil is not the most potent P-gp inhibitor, in fact an analogue of (*R*)-Verapamil, Ro11-2933, **325**, was found to be ten times more potent than (*R*)-Verapamil in reversing resistance to doxorubicin.[57]

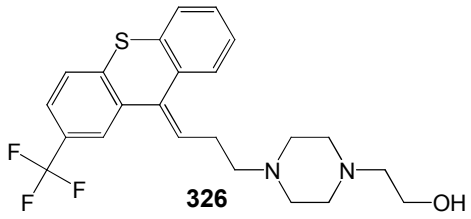


Figure 35: Flupentixol

Calmodulin antagonists are another class of P-gp inhibitors, which includes flupentixol, **326**. Both the *cis* and *trans* isomers of flupentixol are P-gp inhibitors but the *trans* isomer is about four-fold more potent than the *cis* isomer.[58]

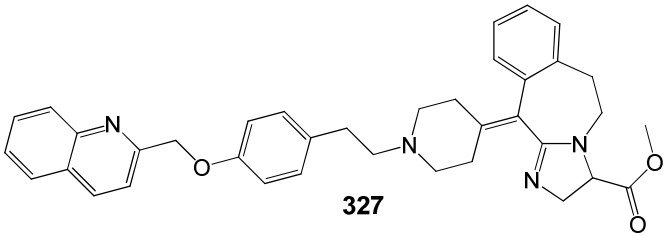


Figure 36: R101933

Also included in this class of P-gp inhibitors is R101933, **327** (figure 36). R101933 is undergoing clinical trials, and was reported in 2002 as being in phase II/III clinical study.[59]

Staurosporine, **328**, and CGP42151, **3279** are two PKCIs that that appear to bind to both ATP binding site (ABS) and steroid-binding hydrophobic region (SBHR).

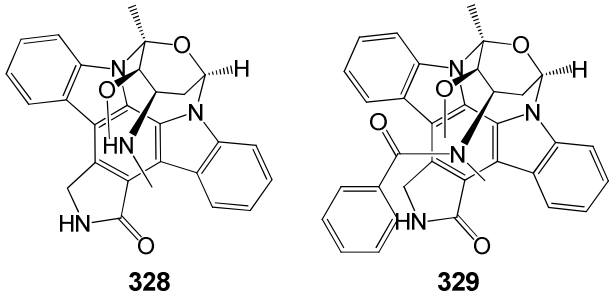
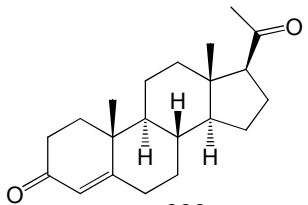


Figure 37: Staurosporine and CGP42151

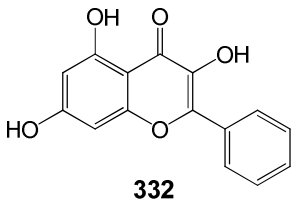
P-gp has been shown to bind reversibly to most steroids, the more hydrophilic steroids are more easily transported and tend to be less useful as P-gp inhibitors. The more hydrophobic (lipophilic) steroids tend to be transported less efficiently and as such are more useful as P-gp inhibitors. Progesterone, **330**, a hormone that occurs naturally in humans, was found to bind to P-gp but appeared not to be transported by P-gp,[60] this indicated the possibility of use as a P-gp inhibitor but from testing it was found to be less effective than (*R*)-Verapamil.



330

Figure 38: Progesterone

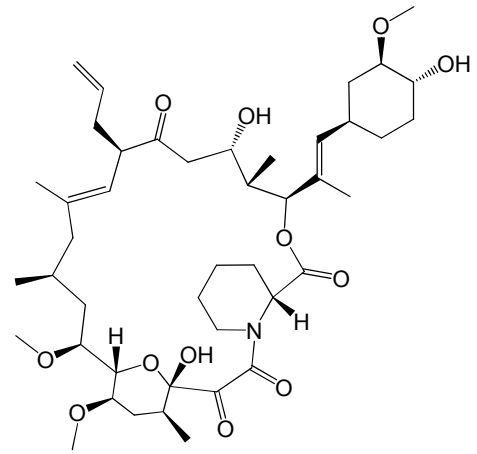
Other steroidal P-gp inhibitors have been tested, such as megestrol acetate and RU486, which have proved to be more effective inhibitors of P-gp than progesterone but only as effective as (*R*)-Verapamil. Flavanoids have also been reported to be P-gp inhibitors that bind to ABS and a vicinal SBHR within a cytosolic domain of P-gp.[61] One such example of this is galangin, **332**.



332

Figure 39: Galangin

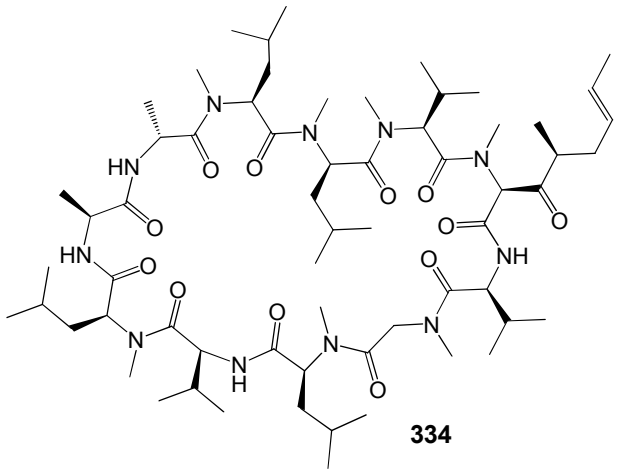
Cyclic peptides, CysA, and macrolide compounds, tacrolimus, **333**, and sirolimus, are immunosuppressants used in organ transplantation and can also act as P-gp inhibitors.[61]



333

Figure 40: Tacrolimus

PSC-833, **334**, is a cyclosporine analogue that is an effective P-gp inhibitor. It has been in two phase III clinical studies, one reported in 2002[62] and one in 2006.[63]



334

Figure 41: PSC-833

Polycyclic alkaloids have also been reported to act as P-gp inhibitors, but because of their cytotoxicity or other intrinsic pharmacological effects almost all of them have been proven to be unsuitable for clinical use as P-gp inhibitors. Also polymer excipients like poly(ethylene)-glycol (PEG300) (20 %, v/v) was reported to produce complete inhibition of P-gp in Caco-2 and MDR1-MDCK cell monolayers.[64]

In this short review of P-gp inhibitors a few illustrative examples of P-gp inhibitors have been given. These examples show the diversity of the structures which have been shown to act as P-gp inhibitors. To date a complete structure activity relationship study of each class of P-gp inhibitors has not been carried out. Instead Wang *et al.* has compiled a list of requirements that potential P-gp inhibitors should have. This list has been compiled for a large group of compounds that has been split into seven classes and is not specific to any one class. There are proven exceptions to this list of

requirements including PEG300 which does not have any tertiary nitrogen. Within the examples given in this review there are two macrocycles which are of different ring size and structural backbone highlighting the possibility that other macrocycles may also act as P-pg inhibitors. Within the classes of P-gp inhibitors there is the calcium blockers classification; therefore it is possible that compounds which bind to calcium may affect the calcium channel.

1.3 Conclusion

In this chapter it has been shown that the typical synthesis of chiral crowns and aza-crowns is long and can often result low yields. Chapter two will demonstrate the efforts in this project towards the development of a short method for the synthesis of achiral macrocycles with high yields for the optimised derivatives. Chapter three will describe the efforts to apply the short methods to the synthesis of the chiral crown ethers containing opiates. Binding studies with some of the chiral crown ethers and studies using these crowns as catalysts have also been outlined. The binding studies carried out in this project are described in chapter four.

Also a brief review with some illustrative examples of P-gp inhibitors has been given. A selection of the products synthesised in this project were tested for their activity as P-gp inhibitors. This work will be detailed in chapter five of this thesis.

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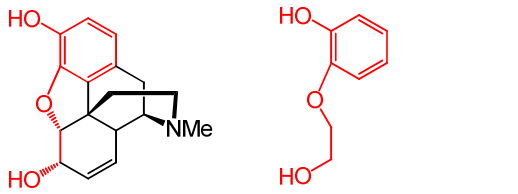
Chapter 2

Synthesis of Macrocyclic compounds containing the 2-(2-hydroxyethoxy)phenol moiety and the precursors to these macrocycles

2.1 Introduction:

This chapter details the synthesis of a series of novel macrocycles and their precursors. The synthesis of these compounds was performed with the idea that the methods developed for their synthesis could then be employed in the preparation of the analogous alkaloid containing macrocycles. Using this approach, the time of the method development for the alkaloid containing derivatives was expected to be significantly reduced. The goal of the project was the synthesis of alkaloid containing crown ethers but prior to their attempted synthesis a model study was carried out. The method development could be carried out with 2-(2-hydroxyethoxy)phenol, **336**, because both the alkaloid derivative, i.e. morphine, and 2-(2-hydroxyethoxy)phenol have two alcohol groups which are expected react in the same preferential order. Figure 42 shows the structural similarities between morphine and the 2-(2-hydroxyethoxy)phenol.



335: Morphine **336**: 2-(2-hydroxyethoxy)phenol

Figure 42: Morphine and 2-(2-hydroxyethoxy)phenol

Although **336** is a subunit of **335**, the pentacyclic **335** is more rigid in structure. The increased rigidity of **335** may lead to difficulties in the macrocyclisation reaction if a flexible backbone is required. This would require extra method development for the synthesis of the macrocycles containing the morphine moiety. Despite this limitation **336** was selected as the model compound.

Although the macrocycles and the *bis*-alcohols and *bis*-phenols to be discussed in this chapter were primarily to be synthesised as a method development tool, they are novel compounds in there own right. Their potential uses were examined later in the project through metal binding and biological analysis, the testing methods and results from these tests will be discussed in chapters four and chapter five respectively. The *bis*-

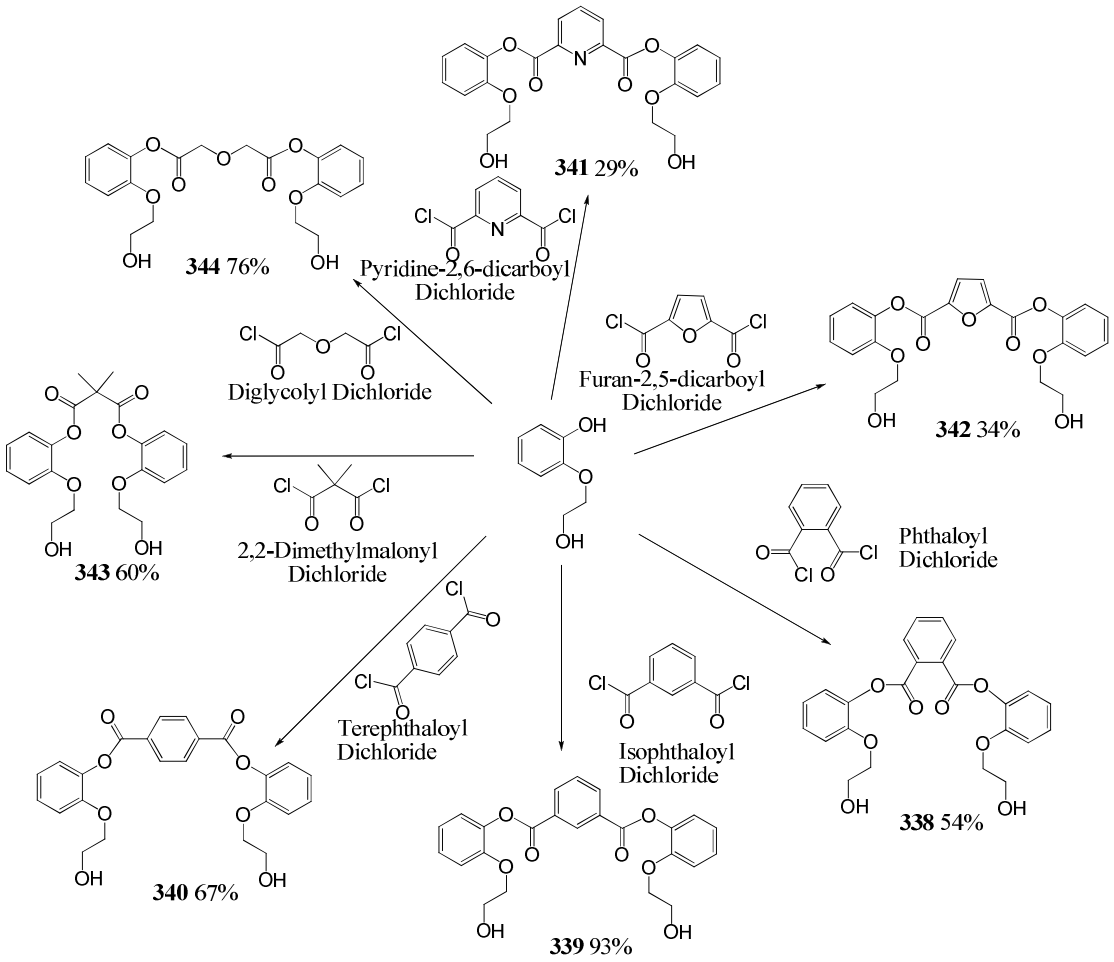
alcohols and *bis*-phenols, compounds **338**-**347**, also underwent the same testing as the crown ethers and results will be discussed in the same chapters.

Also discussed in this chapter is the optimisation of the synthesis of compound **360**. This optimisation was carried out so that the optimised method for the synthesis of this compound could be employed in the synthesis of the analogous alkaloid macrocycle.

2.2 Synthesis of the *bis*-alcohols 338-344:

There were seven diacid dichlorides used to synthesise the *bis*-alcohols; terephthaloyl dichloride, isophthaloyl dichloride, phthaloyl dichloride, 2,2-dimethylmalonyl dichloride, diglycolyl dichloride and 2,6-pyridine dicarbonyl dichloride were commercially available and while furan-2,5-dicarbonyl dichloride was synthesised. Furan-2,5-dicarbonyl dichloride was synthesised by the dehydration of mucic acid to give the diacid[65] followed by chlorination with thionyl chloride under reflux to yield the dichloride species.

Seven *bis* alcohols (**338**-**344**) containing different linkers between the phenolic hydroxy groups were generated. The structure of each of these compounds and their synthesis is given in scheme 23.



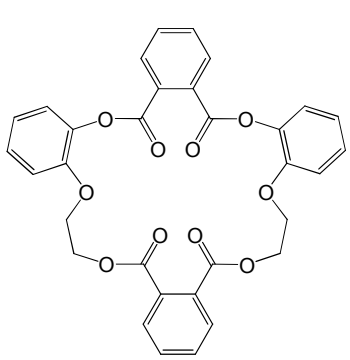
Scheme 23: The synthesis of the seven bis-alcohols.

338-**344** were generated via the reaction of a diacid dichloride with the 2-(2-hydroxyethoxy)phenol at -15 ^{o}C in the presence of triethylamine under nitrogen.

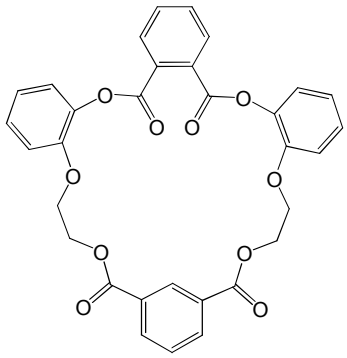
Yields of the *bis*-alcohols ranged from 29 % to 93 %. **339** (93 % yield) gave the highest isolated yield with purification via recrystallisation. **341** (29 % yield), which gave the lowest yield, and **343** (60 % yield) required column chromatography on a silica stationary phase. **338** (54 % yield), **340** (67 % yield), **342** (34 % yield) and **344** (76 % yield) required column chromatography on a silica stationary phase followed by recrystallisation for purification.

2.3 Synthesis of the macrocycles from *bis*-alcohols in section 2.2.

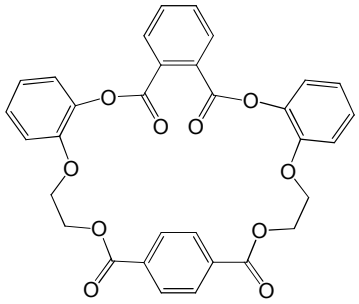
From each of the *bis*-alcohols, **338**-**344**, attempts were made to synthesise at least one macrocycle. From this there was a series of seven macrocycles successfully isolated. The structures of these seven macrocycles are given in figure 43.



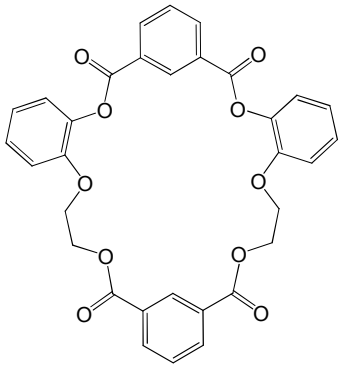
348 (3.2%)



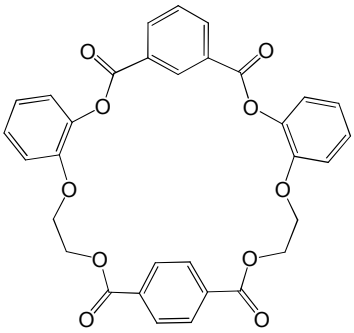
349 (1.9%)



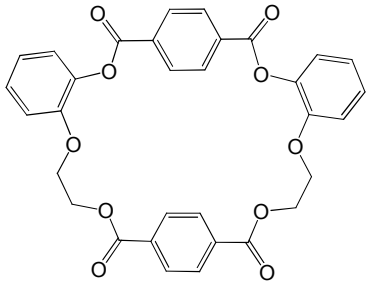
350 (3.7%)



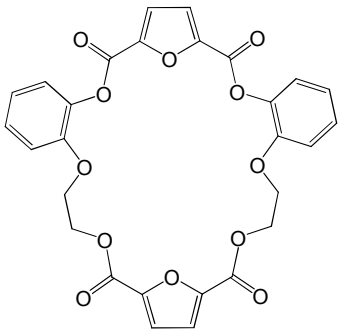
351 (4.4%)



252 (3.5%)



353 (2.5%)



354 (12%)

Figure 43: Macrocycles made from the bis-alcohols.

A general methodology for the synthesis of the macrocycles was employed; reactions were carried out under high dilution conditions in the presence of a base and under a nitrogen atmosphere. The base for each of the successful reactions was triethylamine. Three macrocycles were successfully synthesised from *bis*(2-(2-hydroxyethoxy)phenyl) phthalate, **338.** Reaction of **338** with phthaloyl dichloride, isophthaloyl dichloride and terephthaloyl dichloride yielded **348** (3.2 %), **349** (1.9 %) and **350** (3.7 %) respectively. Two macrocycles were successfully synthesised from *bis*(2-(2-hydroxyethoxy)phenyl) isophthalate, **339**. Reaction of **339** with isophthaloyl dichloride and phthaloyl dichloride yielded **351** (4.4 %) and **352** (3.5 %) respectively. *Bis*(2-(2-Hydroxyethoxy)phenyl) terephthalate, **340**, was reacted with terephthaloyl

dichloride to yield **353** (2.5 %) and *bis*(2-(2-hydroxyethoxy)phenyl) furan-2,5-dicarboxylate was reacted with furan-2,5-dicarbonyl dichloride to yield **354** (12 %). Each of these compounds were isolated and characterised by NMR, high resolution MS, FTIR and melting point. The remaining material from each of the reactions is a mixture of polymer and unreacted starting material.

There were six macrocycles (figure 44) that were not successfully isolated via method using the *bis*-alcohols. The material isolated from these reactions was polymeric structures and unreacted starting materials.

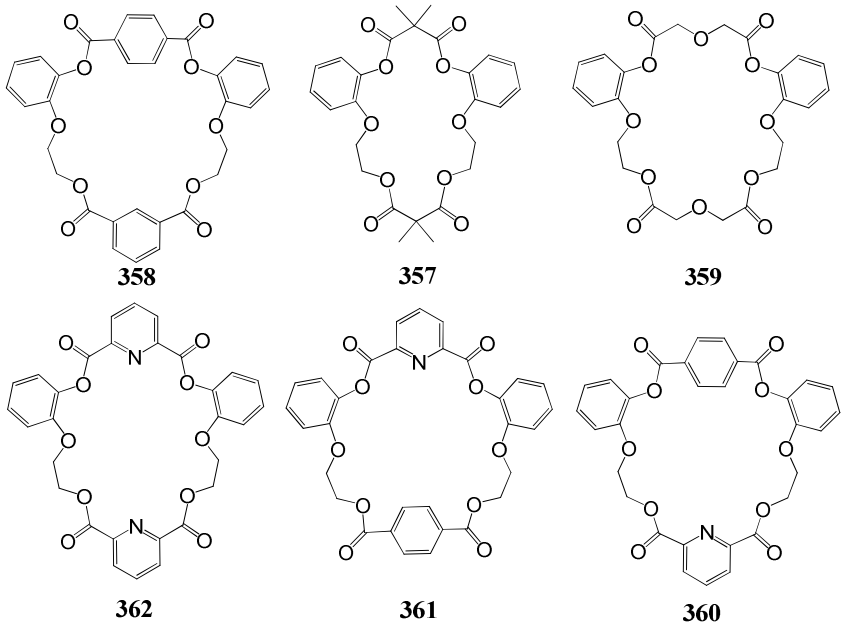


Figure 44: Macrocycles not isolated by this method

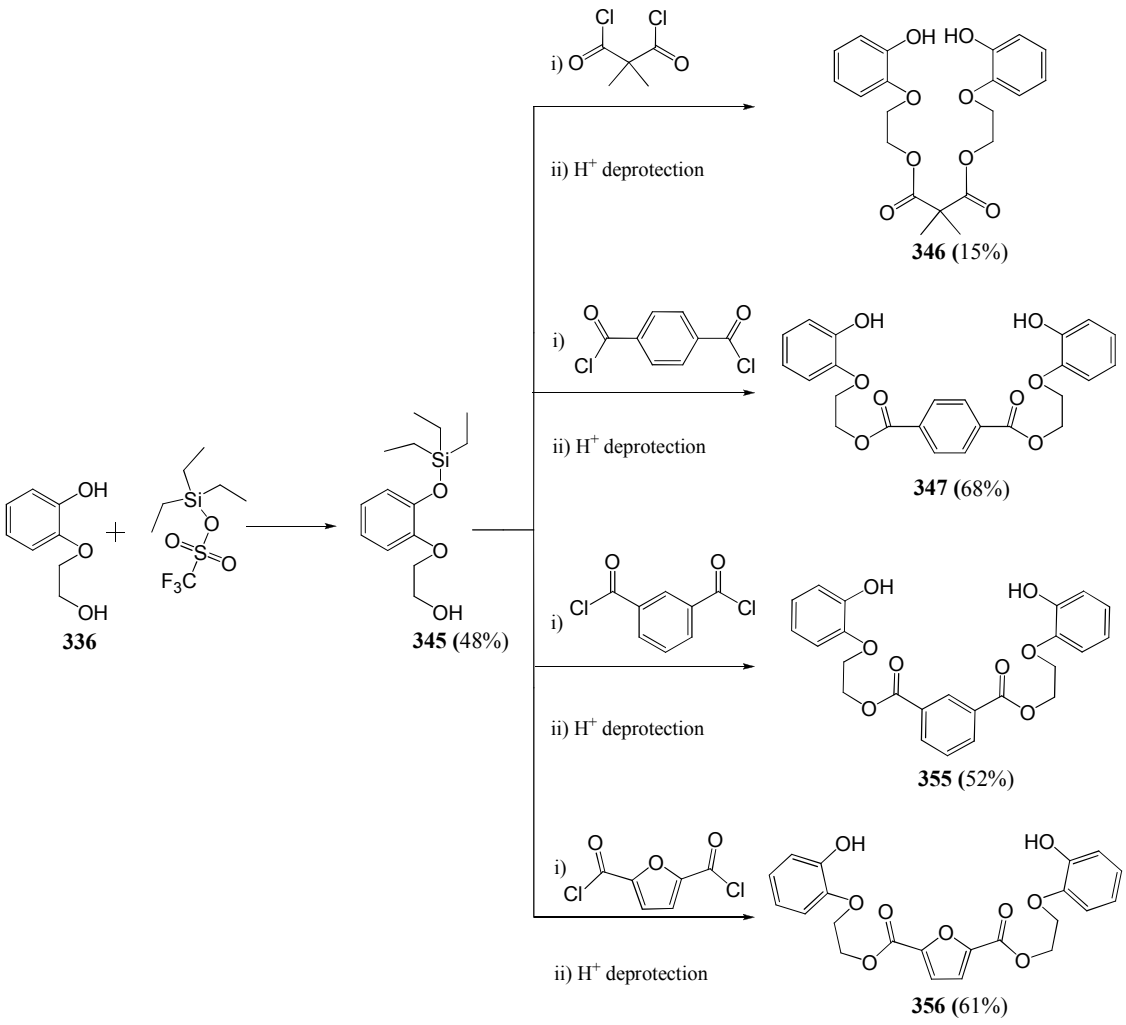
For each attempt the same general method used in the synthesis of **348**-**354** was utilised. The changes that were made to the general method included variation of the base used, concentration of starting materials, temperature and the purification methods in attempts to isolate these six macrocycles. Each attempted synthesis was carried out using five equivalents of the following bases: triethylamine; sodium carbonate; potassium carbonate; and dimethyl amino pyridine. The attempted syntheses were also carried out at room temperature, -15 ^{o}C and in refluxing dichloromethane (40 ^{o}C). The concentrations used were 10 mmol, 40 mmol and 80 mmol. Samples from each reaction were taken and attempts were made to purify them via recrystallisation, column chromatography and distillation using a Kugelrohr apparatus. After numerous unsuccessful attempts at the synthesis of these macrocycles it was decided to synthesise these macrocycles by different methods. These

macrocycles were isolated by other methods discussed later in this chapter, sections 2.5 and 2.6.

2.4 Synthesis of the *bis*-phenols, 346, 347, 355 and 356:

Four *bis*-phenols were synthesised as shown in scheme 24. *Bis*(2-(2-hydroxyphenoxy)ethyl) 2,2-dimethylmalonate, **346**, was the first prepared. **346** was prioritised as results obtained from the biological screening of **357** and **343,** to be discussed in chapter 5, made **346** an important target as part of a structure activity relationship study. **346** was utilised to make **357** which served as a comparison of methods to the methods for the synthesis of the same macrocycle discussed in sections 2.3 and 2.6. Subsequently, *bis*(2-(2-hydroxyphenoxy)ethyl) terephthalate, **347**, *bis*(2-(2-hydroxyphenoxy)ethyl) isophthalate, **355**, and *bis*(2-(2-hydroxyphenoxy)ethyl) furan-2,5-dicarboxylate, **356**, were synthesised by the same method as *bis*(2-(2-hydroxyphenoxy)ethyl) 2,2-dimethylmalonate, **346**.

The method used for synthesis of these products (scheme 24) started with the protection of the phenol with the triethylsilyl (TES) protecting group. The synthesis involved reacting TES triflate with 2-(2-hydroxyethoxy)phenol under nitrogen atmosphere at -15 ^{o}C in the presence of triethylamine.

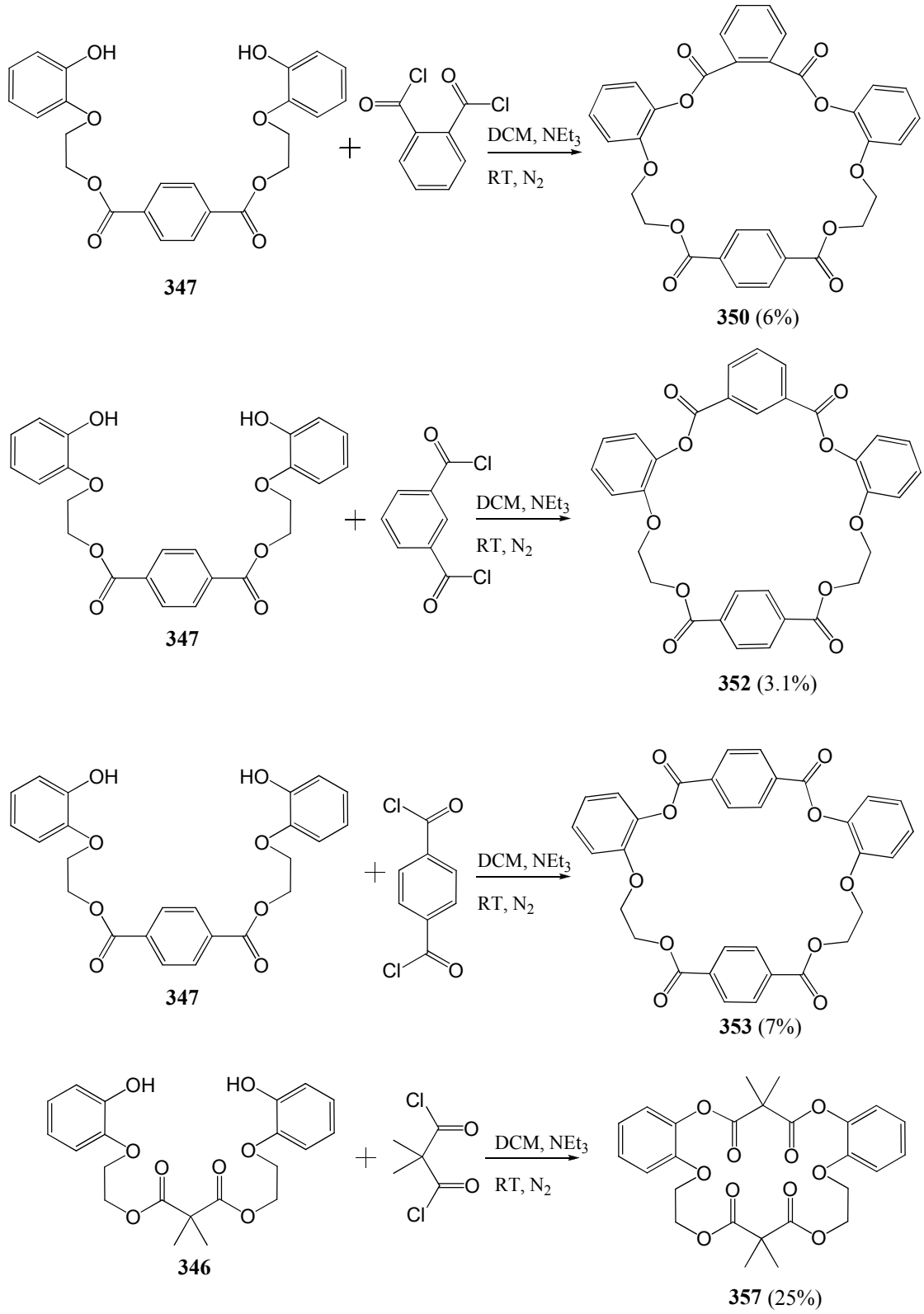


Scheme 24: The synthesis of the bis-phenols

345 was then reacted with a diacid dichloride and the resulting intermediates had column chromatography on a silica stationary phase with a 3:1 diethylether:chloroform mobile carried out to increase purity but were not isolated pure. The TES protected intermediates were subjected to acidic deprotection to give the target *bis*-phenols.

2.5 Synthesis of macrocycles 350, 352, 353 and 357 from *bis*-phenols 346 and 347.

Four macrocycles, **350**, **352**, **353** and **357**, were synthesised from the *bis*-phenols for comparison of yields with the previous method outlined in section 2.3. If the yields from this method were higher than attained in section 2.3 it may be an alternative route for the generation of the alkaloid macrocycles. The method used in this section, scheme 25, was essentially the same as that used for synthesising the macrocycles from the *bis*-alcohols, the main difference being the starting material.



Scheme 25: Synthesis of compounds **350**, **352**, **353** *and* **357**

The yields obtained for **353**, **350** and **357** by this method are higher than that presented in section 2.3. For **353** the yield increased from 2.5 % to 7 % and **350** increased from 3.7 % to 6 %. The most significant difference is that **357**, which was not isolated from

the method in section 2.3, was successfully isolated in 25 % yield. For the final macrocycle isolated by this method, **352**, the yield was slightly less, decreasing from 3.5 % to 3.1 %. Attempts were also made at the isolation of **361** via this method but all attempts were unsuccessful.

2.6 One pot synthesis

Using the one pot method for the synthesis of the macrocycles, 2-(2-hydroxyethoxy)phenol is reacted with half an equivalent of a diacid dichloride and then after an allotted time another half equivalent of a diacid dichloride is added to the reaction. The synthesis outlined out in this section was undertaken for two reasons; 1) as a comparison to the previous methods, sections 2.3 and 2.5, and 2) to try to synthesise some of the macrocycles that had not been successful by the previous methods.

A total of ten macrocycles, **351**, **352, 353, 354, 357, 358**, **359**, **360**, **361** and **362**, were successfully synthesised by this method. Scheme 26 gives the general method employed using the example of **358**. Five of the ten macrocycles, **358**, **359**, **360**, **361** and **362** (figure 45) were only synthesised by this method and attempts to isolate them via the methods in sections 2.3 and 2.5 failed.

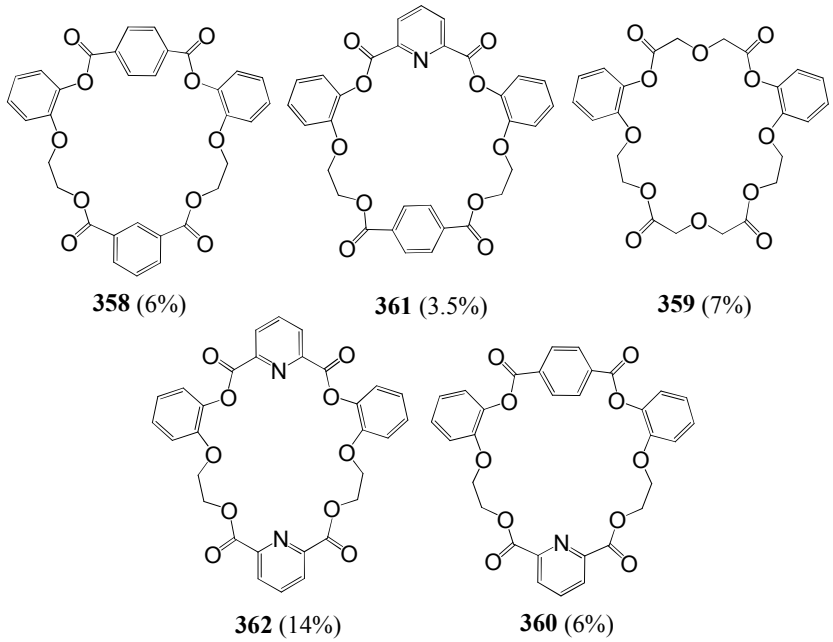
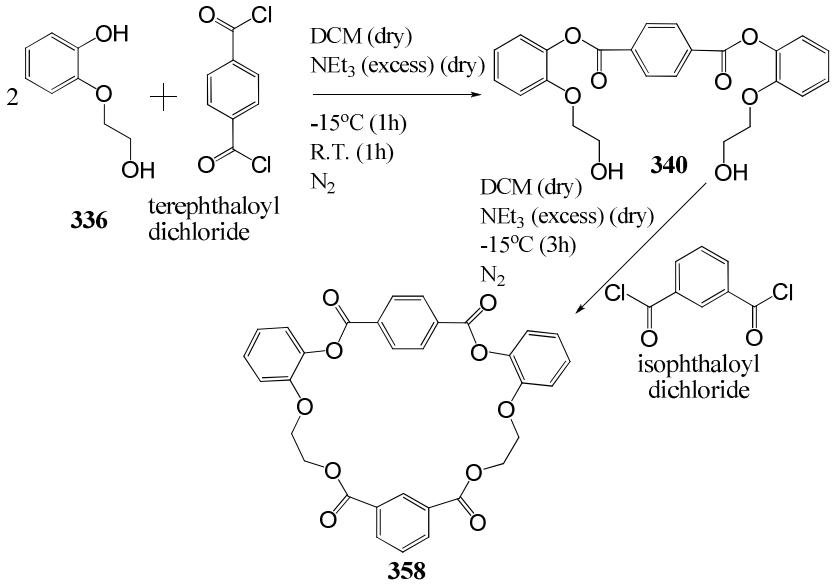


Figure 45: Five macrocycles isolated solely by the one pot method

Each of the macrocycles in figure 45 were isolated and characterised by NMR, high resolution MS, FTIR and melting point, with the exception of compound **361** which was sparingly soluble in all available solvents (acetone, acetonitrile, benzene, butanol,

carbon tetrachloride, chloroform, cyclohexane, 1,2-dichloroethane, dichloromethane, diethylether, N,N-dimethylformamide, dimethylsulphoxide, 1,4-dioxane, ethanol, ethylacetate, hexane, methanol, pentane, petroleum ether, propanol, pyridine, tetrahydrofuran, toluene, water and xylene) and as such the ^{13}C NMR could not be recorded.

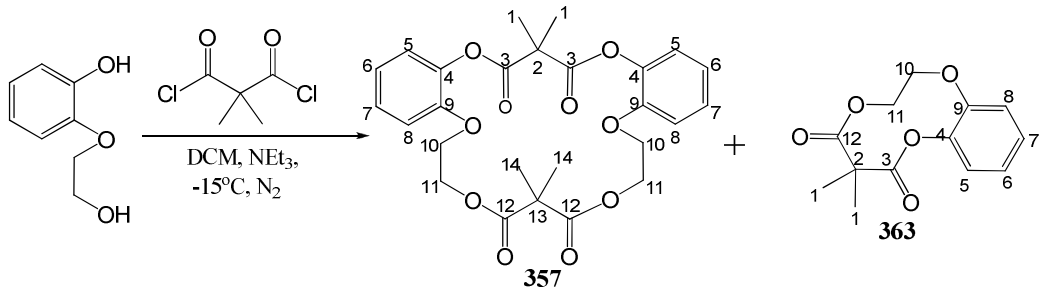
Scheme 26 shows the synthetic pathway of a macrocycle, **358**. All the other derivatives in this section were synthesised via the same general method with variation of the dichlorides and the base used, as detailed in the experimental section of this chapter.



Scheme 26: Synthesis of **358**

The five macrocycles synthesised via this method and in sections 2.3 and 2.5 are **351**, **352**, **353**, **354** and **357**. Their yields are 23 %, 16 %, 2.5 %, 9 % and 2.5 % respectively. A significant improvement in yield was seen for **351** and **352** via method. **353** was isolated in equivalent yields to that obtained in section 2.3. A decreased yield of **354** and **357** was recorded in this section, although this decrease was less significant for compound **354** than for compound **357**.

The first attempt at the synthesis of **357** resulted in a yield of 2.1 % (0.015 mmol, 8 mg). The X-Ray crystal structure showed that the target product was not synthesised and instead compound **363** was isolated, as shown in scheme 27 below. Due to the small amount of **363** obtained there was not enough material to record the other data required (melting point, mass spectrum and infra-red spectrum). In order to record the full characterisation data the synthesis was repeated on a larger scale, with a yield of 2.5 % (0.12 mmol, 57 mg) recorded, reported in the experimental section.



Scheme 27: Synthesis of **357** *and* **363**

Both proton and carbon NMR of the product from repeated synthesis were recorded and agreed with the NMR data from the original synthesis. From this the full characterisation data (NMR, IR, HRMS and melting point) was recorded.

The predicted values of the NMR, both ^{1}H and ^{13}C, for compounds **357** and **363** are listed in the table 1 below alongside the NMR data recorded from the product. Predictions were carried out using ChemBioDraw Ultra Version 11.0.1 © 1986-2007 CambridgeSoft.

Atom Number	357		363		Product	
	^{1}H Prediction	^{13}C Prediction	^{1}H Prediction	^{13}C Prediction	^{1}H	^{13}C
1	1.37	22.8	1.42	22.8	1.53	20.96*
2		51.3		51.7		50.95*
3		171.5		171.5		170.81
4		142.0		142.0		142.82
5	7.18	120.6	7.18	120.6		124.45
6	6.98	120.7	6.98	120.7		124.69
7	7.15	126.1	7.15	126.1		127.33
8	6.96	114.8	6.96	114.8	7.02-	123.25
9		153.9		153.9	7.14	150.77
10	4.22	67.0	4.33	71.9	4.05	64.03
11	4.50	67.3	4.50	67.3	4.48	72.54
12		174.5		174.5		172.70
13		52.1				50.95*
14	1.47	22.8			1.53	20.96*

Table 1*: Predicted values for ^{1}H and ^{13}C NMR of macrocycles* **357** *and* **363** *compared to that recorded for the product. * Individual peaks are not observed for Carbon 1 and 14 and for Carbon 2 and 13 in the product.*

From the NMR predictions, **357** and **363** are quite similar by NMR, but there are differences predicted in both carbon and proton NMR. Most notably there should be an extra peak in the proton NMR spectra of **357** over that of **363** for H14 and also in the carbon NMR spectra for C13. C13 in structure **357** is different from that of C2 **357** because of its location is between two ester groups synthesised from the aliphatic alcohol groups of 2-(2-hydroxyethoxy)phenol and C2 is between two ester groups synthesised from the phenols of 2-(2-hydroxyethoxy)phenol. Each of these peaks should differ from that of C2 in **363** as this carbon is located between two different ester groups, one of the phenol and the other from the aliphatic alcohol. Also the peaks for H's 10 and 11 should be closer to each other in **363** relative to **357** with the peaks for C's 10 and 11 should be closer to each other in **357** relative to **363**. From comparison of the predicted NMR spectra of both products with that of the isolated product it appears that the product isolated was **363**, as the number of peaks is in

accordance with the predicted number of peaks for **363**. Although the NMR spectra are predicted to be very similar and could appear to be the same, as indicated by the prediction of C1 and C14 of **357** being identical to C1 of **363** although the predicted values for the hydrogens on these carbons are predicted to be different.

As the NMR spectra of **357** and **363** appear to be the same, the next method to show the difference would be mass spectrometry, as there is a clear difference in the mass of the two macrocycles. The exact mass of **357** has been calculated to 500.1682 amu and the exact mass of **363** has been calculated to exactly half of that of **357** at 250.0841 amu. The mass spectrum of the first sample that was submitted for X-ray, was not recorded as the entire sample went for X-ray. The compound isolated from the second synthesis was purified and submitted for time of flight, mass spectrometry. The exact mass was recorded at 501.1746 amu which is within error of the calculated mass of protonated **357**, 501.1755 amu, as seen in figure 46 below.

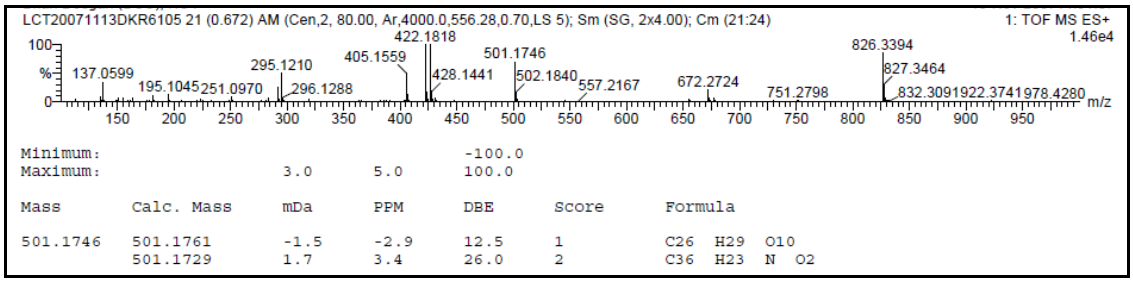


Figure 46: TOF MS of **357**.

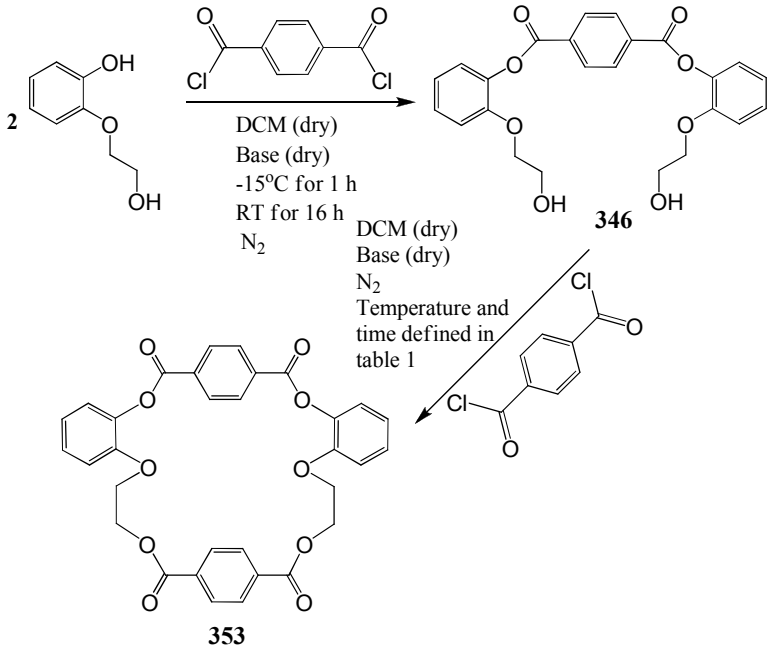
This indicates that although there may be a small impurity of **363** in the sample the sample was mainly the expected product, **357**. Attempts were made, unsuccessfully, to grow crystals of this product from the slow evaporation of the following solvents (both as mixed solvent systems and individual solvents): chloroform, hexane, dichloromethane, acetonitrile, acetone, ethylacetate, diethylether and cyclohexane.

We postulated that **363** is a minor product and then repeated the synthesis to try to isolate **363** in enough yield for full characterisation. Multiple attempts, using the same method, to generate **363** again failed. Each time the mass spectrum, although at a lower resolution using an Agilent Technologies 6110 Quadrapole LC-MS, indicated the presence of **357** as the product. The X-Ray data will be discussed in section 2.9.

2.7 Optimisation of the one pot synthesis of compound 353:

At this stage of the project the optimisation of the one pot synthesis of **353** was undertaken as this improved method could then be utilised in attempts to isolate the analogous macrocycle containing the morphine moiety.

Optimisation was carried out by changing the reaction conditions and repeating the reaction until a reasonable yield was isolated and proved repeatable. After a series of reactions were carried out the data from these reactions was used in Design Expert® version 6.0.10 from Stat-Ease Inc. This is a statistical anyalysis program that carrys out calculations on results obtained from previous synthesis and then suggests optimial conditions to try. The reaction is outlined in scheme 28 below.



Scheme 28: Optimisation of the synthesis of **353**

The same general method was employed as outlined earlier in section 2.6 with variation of temperature, concentration, type of base, amount of base, and time individually and in conjunction with one another until the reaction was deemed to be reproducible and of high yield.

The general method for optimisation of yield of **353** is outlined below:

2-(2-Hydroxyethoxy)phenol (154 mg, 1.00 mmol) was dissolved in dry DCM (10.0 mL) at room temperature under nitrogen and then chilled to -15 ^{o}C. Dry base [table 2 (**A**)] is added while stirring and maintaining the temperature at -15^{o}C. Terephthaloyl dichloride (100 mg, 0.50 mmol) was then dissolved in dry DCM (5.0 mL) and added to the reaction mixture. The reaction mixture was then stirred for 1 hour and after

which it was allowed to warm to room temperature and was stirred for sixteen hours, as this was the same time scale in which the intermediate product, *bis*(2-(2-hydroxyethoxy)phenyl)terephthalate, was synthesised. Dry base [table 2 (**B**)] and dry DCM [table 2 (**C**)] were then added to the reaction flask. The contents of the flask were heated or cooled to the required temperature set in table 2. Terephthaloyl dichloride (100 mg, 0.50 mmol) was dissolved in dry DCM indicated [table 2 (**D**)] and added slowly to the reaction flask. This reaction mixture was then stirred for a time dictated in table 2. The reaction was quenched via addition of DI water (10.0 mL) and warmed to room temperature and stirred for ten minutes. The reaction mixture was then transferred to a separation funnel and the organic and aqueous layers were separated. An NMR of the crude products was recorded, and from this an approximation of yield, by ratio of product to unwanted side-products, was made, the products of the higher yielding reactions were then purified by column chromatography on a silica stationary phase to give pure isolated yields. The unwanted side-products where the intermediate, *bis*(2-(2-hydroxyethoxy)phenyl)terephthalate, and some polymer product. These isolated yields are given in table 2.

Reaction	Ratio Product: polymer: **340**	Base used		Equivalents base used		Volume DCM added at **C**	Volume DCM added at **D**	Temp. (°C)	Time (h)
		A	**B**	**A**	**B**				
A	**1:0.9:0.5**	NEt_3		3.2	3.2	70	15	-15	3
B	**1:2:0.5**			3.2	3.2	0	15	-78	3
C	**1:1:4**			3.2	3.2	70	15	-78	3
D	**1:1:0.3**			3.2	3.2	70	15	RT	3
E	**1:1:0.5**			3.6	3.6	80	105	RT	3
F	**0:0:1**	K_2CO_3		2.8	2.8	70	15	RT	3
G	**1:1:0.2**	NEt_3	K_2CO_3	2.4	2.8	70	15	RT	3
H	**1:1:12**	Cs_2CO_3		2.2	2.2	45	50	RT	3
I	**1:1.5:4**	NEt_3	Cs_2CO_3	2.2	2.2	40	55	RT	3
J	**1:3:4**	tetramethylethane-1,2-diamine		2.8	2.8	40	55	RT	3
K	**1:2.5:12**	iPr_2NH		2.8	2.8	40	55	RT	3
L	**1:2:3.4**	iPr_2NH	NEt_3	4.2	2.2	40	55	RT	3
M	**4:3:8**	iPr_2NH		2.8	2.8	40	55	RT	24
N	**4:1.6:2.4**	Na_2CO_3		2.8	2.8	40	55	RT	3
O	**1:1:1**	NEt_3	Na_2CO_3	2.2	2.8	40	55	RT	3
P	**1:0:2.5**	Na_2CO_3		5.6	5.6	40	55	RT	3
Q	**1:1:20**			2.8	2.8	40	55	RT	24
R	**1:0.4:1.2**			2.8	2.8	40	55	-15	3
S	**1:0.3:0.6**			2.8	2.8	40	55	40	3
T	**1:0:1.5**			2.8	2.8	0	15	RT	3
U	**1:0:1.3**			2.8	2.8	40	55	RT	3
V	**1:0:8**			2.8	2.8	100	85	RT	3
W	**1:2:2**			5.6	5.6	0	15	40	3
X	**1:0.3:0.3**			5.6	5.6	40	45	40	3
Y	**1:0.2:2.2**			2.8	2.8	0	15	40	3
Z	**1:0.2:0**			4.2	4.2	60	50	40	3
AA	**1:0:13**			17	17	70	65	40	3
AB	**1:0.2:3.8**			11	11	60	50	40	3
AC	**1:0:30**			18	18	60	50	40	3
AD	**1:0.5:0.2**	NEt_3		2.5	2.5	60	50	40	3
AE	**1:1:3**			0.8	0.8	60	50	40	3
AF	**1:0.9:0.9**			3.6	3.6	60	50	40	3
AG	**1:1:0.4**			2.5	2.5	35	50	40	3
AH	**1:1:0.1**			2.5	2.5	75	50	40	3

Table 2: Conditions screened in optimisation of the synthesis of **353**

Reaction	Approximate yield from ratios on NMR of first attempt at the reaction	Yield isolated
A	41.6%	38.2%
D	43.5%	28.3%
E	40.0%	14.8%
X	62.5%	0%
Z	83.0%	0%
AD	58.8%	44%

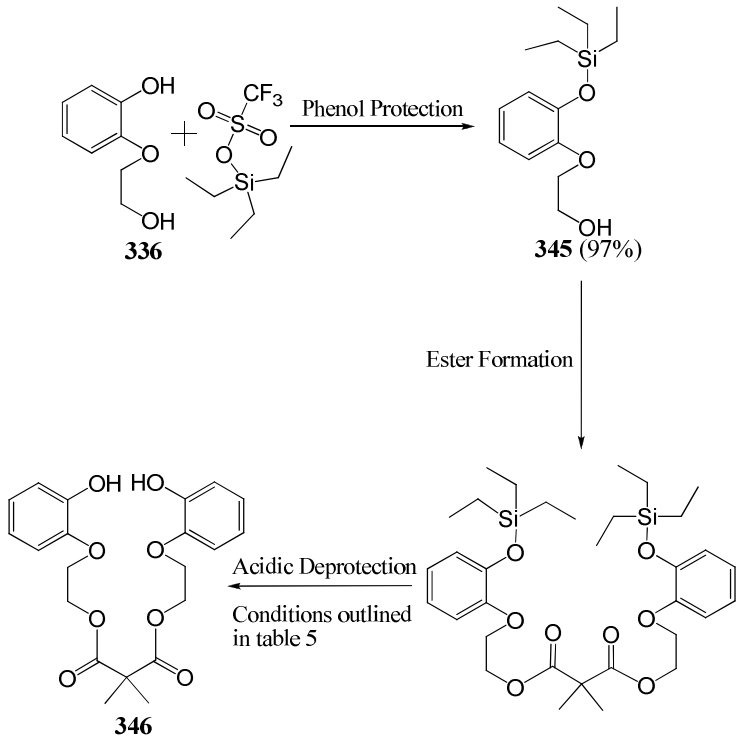
Table 3: Isolated yields from optimisation reactions.

The target product was not recovered from the columns of the crude products from reactions X and Z, even though by TLC the product should have eluted from the column with the same R_f as achieved with the products from the other reactions. Reactions X and Z were repeated a further three times and each time the reactions failed to produce the same ratio of product to the intermediate and the polymer as was achieved in the first reaction, with approximate yields from NMR being less than 20% for each repeated attempt at the synthesis. This shows that the reactions X and Z were

not reproducible and for this reason it was decided to use triethylamine as the base for optimisation as the product was isolatable when triethylamine was used as seen in reactions A, D and E. Reaction AD was repeated in triplicate and the isolated yield given in table 3 was the average of the three reactions (individual yields were 44.2 %, 45.3 % and 42.5 %) and this has a standard de*via*tion of 1.4 %. This indicates that although the reaction is not ideal, as a higher yield may be isolatable using different conditions, the reaction is repeatable with significantly higher yield than that of the original method, 2.5 %. For this reason the conditions used in reaction AD were chosen for use in the synthesis of the morphine macrocycle with terephthaloyl dichloride.

2.8 Optimisation of *bis*(2-(2-hydroxyphenoxy)ethyl) 2,2-dimethylmalonate, 346:

When *bis*(2-(2-hydroxyphenoxy)ethyl) 2,2-dimethylmalonate was initially tested as a P-glycoprotein inhibitor the results indicated this could be a potent inhibitor of the P-glycoprotein efflux pump, see section 5.2.2. As such, more of the compound was required for testing, and the decision was taken to optimise the synthesis of this derivative.



Scheme 29: Reaction Pathway for the synthesis of **346**

The first step optimised was the protection of 2-(2-hydroxyethoxy)phenol. Triethylsilyl triflate was added to 2-(2-hydroxyethoxy)phenol in the presence of triethylamine in dry dichloromethane under an inert atmosphere. It was found that using the same reaction

conditions and extending the reaction time to forty-eight hours from twenty-four hours the yield increased from an initial yield 48 % of to 97 %.

The next step was the optimisation of the synthesis of triethylsilyl protected *bis*(2-(2-hydroxyphenoxy)ethyl) 2,2-dimethylmalonate. The optimisation investigated the effects of time, volume of dichloromethane and the amount of triethylamine used. After only four experiments by increasing the reaction time from four to forty-eight hours, reducing the concentration of the dichloride and increasing the number of equivalents of triethylamine from 2.85 to 3.2 (see table 4) the yield was increased from 77 % to 95 % (triplicate results of 92 %, 95 % and 95 %).

Time (hours)	Volume (mL) of dichloromethane per mmol dimethylmalonyl chloride	Equivalents triethylamine to **345**	Yield (%)
4	24	2.85	77
6	17	2.56	66
24	21	3.20	79
48	21	3.20	95

Table 4: Conditions for optimisation of triethylsilyl protected bis(2-(2-hydroxyphenoxy)ethyl) 2,2-dimethylmalonate

At this stage of the optimisation the triethylsilyl protected *bis*(2-(2-hydroxyphenoxy)ethyl) 2,2-dimethylmalonate could now be isolated in 92 % overall yield which is a significant improvement on the 33 % noted earlier. The final step is the selective removal of the triethylsilyl protection groups. Acidic conditions are used so care has to be taken not to break the ester bonds. TES deprotection was monitored by TLC every ten minutes until the protected *bis*(2-(2-hydroxyphenoxy)ethyl) 2,2-dimethylmalonate was no longer present in solution. The reactions were then stopped and the target product purified. It is important that the reaction can be stopped and the target product separated from the deprotection reagent quickly as the continuation of the reaction could break the ester bonds. Table 5 lists the conditions tried for the deprotection step and the yields isolated from each reaction.

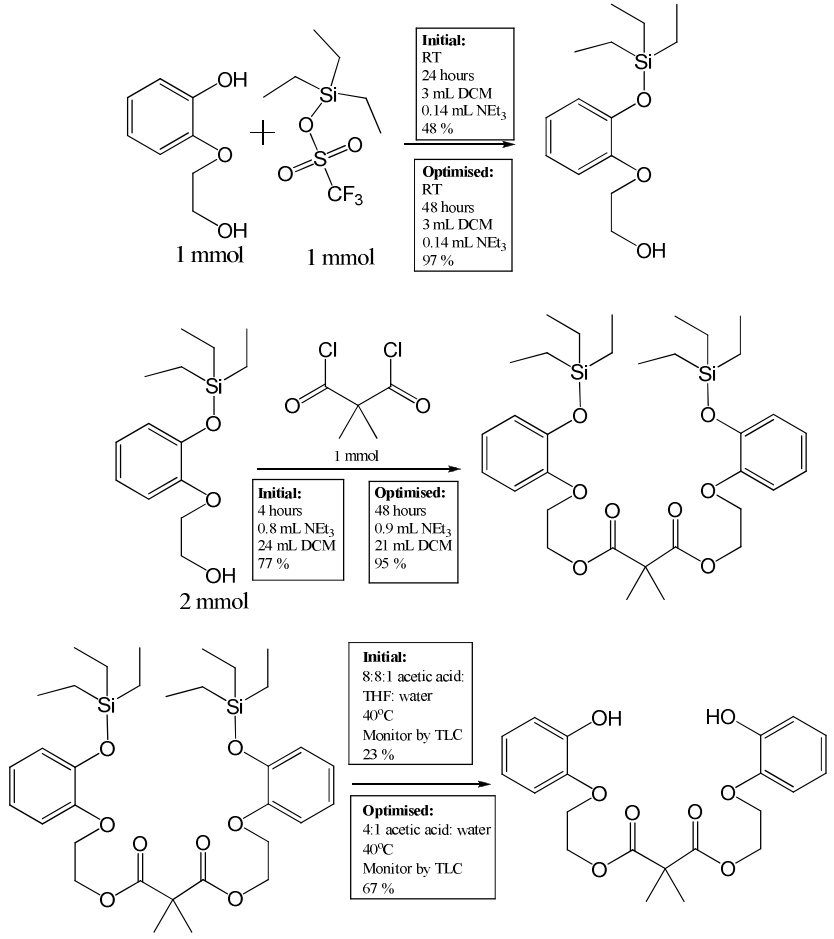
The results in table 5 show that the best conditions for this reaction when using 4:1 acetic acid:water at 40 ^{o}C. This method is postulated to be the best for three principle reasons: 1) The acetic acid is an effective reagent for the hydrolysis of the silyl-ester bond but not so strong as to easily hydrolyse the ester bond. 2) The product is a solid which is not very soluble in water, therefore when the deprotection is complete and the dichloromethane is added the product separates from the acid quickly while the acid is quenched. This differs from reactions 1 and 2 in which the product can be held in

solution with the acetic acid and water by the tetrahydrofuran allowing the acetic long to hydrolyse the ester bond. 3) The purification is less complicated that that of the methods using 2,3-dichloro-5,6-dicyanobenzoquinone (which also gave higher yields than obtained by the original method), as this reagent is partially soluble in dichloromethane and has to be separated by column chromatography, whereas the purification after reaction 10 (table 5) was a recrystallisation.

Reaction	Deprotection conditions	Temp.	Work-up	Yield
1	8:8:1 acetic acid: tetrahydrofuran: water	RT	Addition of Na_2CO_3 saturated water and dichloromethane	23
2	6:6:1 acetic acid: tetrahydrofuran: water	RT	Addition of Na_2CO_3 saturated water and dichloromethane	20
3	1:1 Tetrachloromethane: methanol sonication	40°C	Remove from sonication bath and removed solvents under vacuo	22
4	20 mol% 2,3-Dichloro-5,6-dicyanobenzoquinone in 9:1 acetonitrile: water	RT	Addition of DCM for separation of reactions from the product	47
5	20 mol% 2,3-Dichloro-5,6-dicyanobenzoquinone in 4:1 tetrahydrofuran: water	RT	Addition of DCM for separation of reactions from the product	51
6	2 equivalents potassium fluoride in acetonitrile	80°C	Addition of H_2O extraction with dichloromethane	18
7	2 equivalents potassium fluoride in acetonitrile	RT	Addition of H_2O extraction with dichloromethane	0
8	2 equivalents potassium fluoride and 2 equivalents 18-crown-6 in acetonitrile	80°C	Addition of H_2O extraction with dichloromethane	23
9	2 equivalents potassium fluoride and 2 equivalents 18-crown-6 in acetonitrile	RT	Addition of H_2O extraction with dichloromethane	0
10	4:1 acetic acid: water	40°C	Addition of Na_2CO_3 saturated water and dichloromethane	67
11	tetrabutylammoniun fluoride 1M in tetrahydrofuran	RT	Addition of H_2O extraction with dichloromethane	0

Table 5: *Conditions for optimisation of deprotection of triethylsilyl protected bis(2-(2-hydroxyphenoxy)ethyl) 2,2-dimethylmalonate*

From the optimisation of the synthesis of *bis*(2-(2-hydroxyphenoxy)ethyl) 2,2-dimethylmalonate the overall yield is now 62 % repeatable which is a significant improvement on the 8 % under the original conditions. Scheme 30 shows the optimised method versus the original procedure for the synthesis of **346**.



Scheme 30: Optimised synthesis of **346***, overall yield 62%*

2.9: X-Rays of 352, **353, 363** and **343:**

An understanding of the interactions in the crystals of a potential ion receptor can provide valuable information on the bonding mode and binding sites of "host" molecules in solution studies.[36] The crystallographic analysis of therapeutic compounds has also proven invaluable to chemists and biologists in understanding the key binding sites and modes of action of these therapeutic agents.[66] From the X-ray crystallographic analysis of the macrocyclic structures **352**, **353** and **363,** the cavity sizes of the cyclic species were estimated using Mercury 1.4.2 software. This data was based on solid state and it must be emphasised that the macrocycles may undergo significant conformational changes when in solution or when binding to guest species. However the X-ray data regarding the cavity size of the macrocycles can be used to

estimate which of the guest species might have a significant chance of binding to the macrocycle. In this project the guest species of interest are metal cations. The full data for each of the compounds, in their .cif format files, is given on CD in the appendix. By comparing trends in X-ray data with actual trends of metal cation binding this may lead to a more accurate predictive model for future work.

2.9.1: Discussion of the X-Ray Crystal Structure of **352**

Crystals suitable for single crystal X-ray crystallographic determination of **352** were grown by slow evaporation from chloroform:hexane (1:2), yielding colourless block shaped crystals.

Selected bond distances, torsion angles and angles of non-hydrogen atoms are given in table 6. Table 7 gives selected measurements across the cavity of the macrocycle which are illustrative of the cavity size. Figure 47 shows perspective views of the crystal structure and figure 48 shows the crystal structure with atomic numbering.

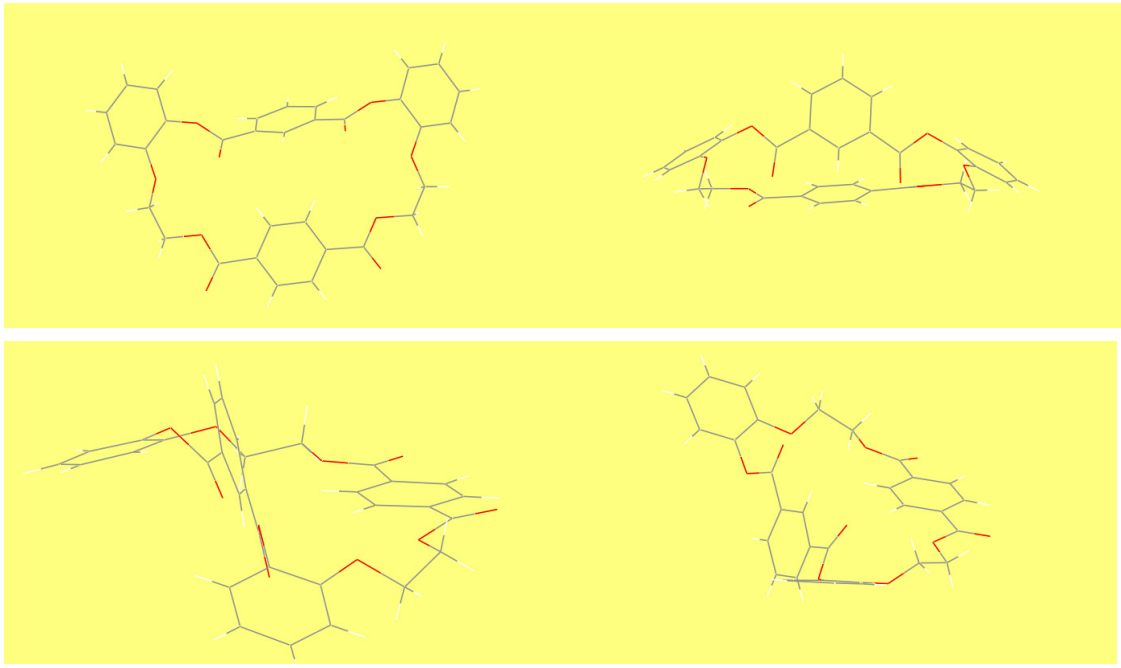


Figure 47: X-Ray crystal structure of **352** *from various aspects*

The presence of the four phenyl rings, severely restrict the flexibility commonly recognized for ethereal aliphatic crown ethers. The structure takes on the form of a flattened and slightly deformed ellipsoid.

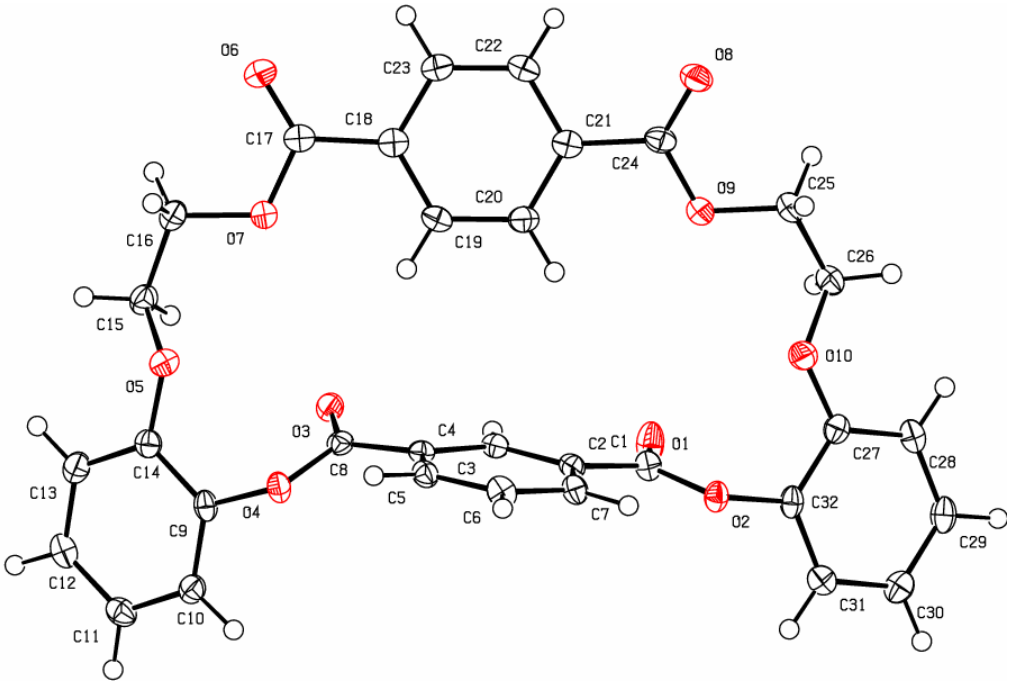


Figure 48: X-Ray crystal structure of **352**

Bond lengths		**Estimated standard deviation**
C(4)–C(8)	1.485 Å	2
C(17)–C(18)	1.492 Å	2
C(14)–O(5)	1.3666 Å	18
O(2)–C(32)	1.4026 Å	17
O(5)–C(15)	1.4334 Å	18
C(16)–O(7)	1.4443 Å	18
O(9)–C(25)	1.4454 Å	19
Bond angles		**Estimated standard deviation**
C(1)–O(2)–C(32)	116.51°	11
C(7)–C(2)–C(1)	122.31°	14
O(4)-C(9)-C(14)	121.87°	13
O(7)-C(17)-C(18)	112.21°	13
C(27)-O(10)-C(26)	116.51°	12
C(16)-C(15)-O(5)	109.86°	13
Torsion angles		**Estimated standard deviation**
C(10)–C(9)–C(14)–O(5)	177.57°	13
O(10)–C(27)–C(32)–C(31)	–177.50°	13
O(2)–C(1)–C(2)–C(3)	–172.58°	13
C(3)–C(4)–C(8)–O(4)	151.51°	13
O(3)-C(8)-C(4)-C(3)	13.0°	2
O(1)-C(1)-C(2)-C(3)	5.8°	2
O(7)-C(17)-C(18)-C(19)	1.9°	2
O(9)-C(24)-C(21)-C(22)	–164. 93°	13
O(6)-C(17)-C(18)-C(19)	–179.23°	15
O(8)-C(24)-C(21)-C(22)	14.9°	2

Table 6: Representative bond lengths, bond angles and torsion angles of **352**.

Macrocycle **352** crystallizes in the monoclinic space group $P2_1/c$ with four independent molecules per asymmetric unit. The bond length for C(4)–C(8) is 1.485 Å and for C(17)–C(18) is 1.492 Å as to be expected as these bonds are similar in nature with the most obvious difference being a meta substituent to the C(4)-C(8) bond and there being a substituent in the para position to the (C17)-(C18) bond in their corresponding phenyl rings. For O(5)–C(15) the bond length is 1.4334 Å with C(15) being sp^3 hybridised and for C(14)–O(5) the bond length is slightly shorter at 1.3666 Å with this reduced bond length caused by the sp^2 hybridisation of C(14). Bonds C(16)–O(7) and O(9)–C(25)are almost the same distances at 1.4443 Å and 1.4454 Å respectively showing that as expected oxygens 7 and 9 are similar as are carbons 16 and 25.

The angle for C(10)–C(9)–C(14) is 121.41° and is close to the C(31)–C(32)–C(27) angle of 121.66°. However, torsion angles for C(10)–C(9)–C(14)–O(5) and O(10)–C(27)–C(32)–C(31) are 177.57° and –176.02° respectively. This gives an indication that the compound is not completely symmetrical in the solid state. The asymmetrical state of the molecule in the crystal is also shown by comparison between torsion angle values associated with the isophthalate unit are similar and equal to 151.51° for C(3)–C(4)–C(8)–O(4) and –172.58° for O(2)–C(1)–C(2)–C(3).

From – To	Distance (Å)
O1 – O7	7.2
O4 – O5	2.8
O3 – O7	3.3
C2 – C20	3.6
O2 – O9	4.6
O2 – O7	8.0
O4 – O9	8.8
O5 – O10	10.1
C16 – C27	11.1

Table 7: Dimensions of the cavity of **352**.

Table 7 details intramolecular distances which are indicative the size of the cavity of macrocycle **352**.

2.9.2: Discussion of the X-ray crystal structure of Compound **353**

Crystals suitable for single crystal X-ray crystallographic determination of **353** were grown by slow evaporation from chloroform:hexane (1:1), yielding colourless block shaped crystals.

Selected bond distances, torsion angles and angles of non-hydrogen atoms are given in table 8. Table 9 gives selected measurements across the cavity of the macrocycle

which are illustrative of the cavity size. Figure 49 shows perspective views of the crystal structure and figure 50 shows the crystal structure with atomic numbering.

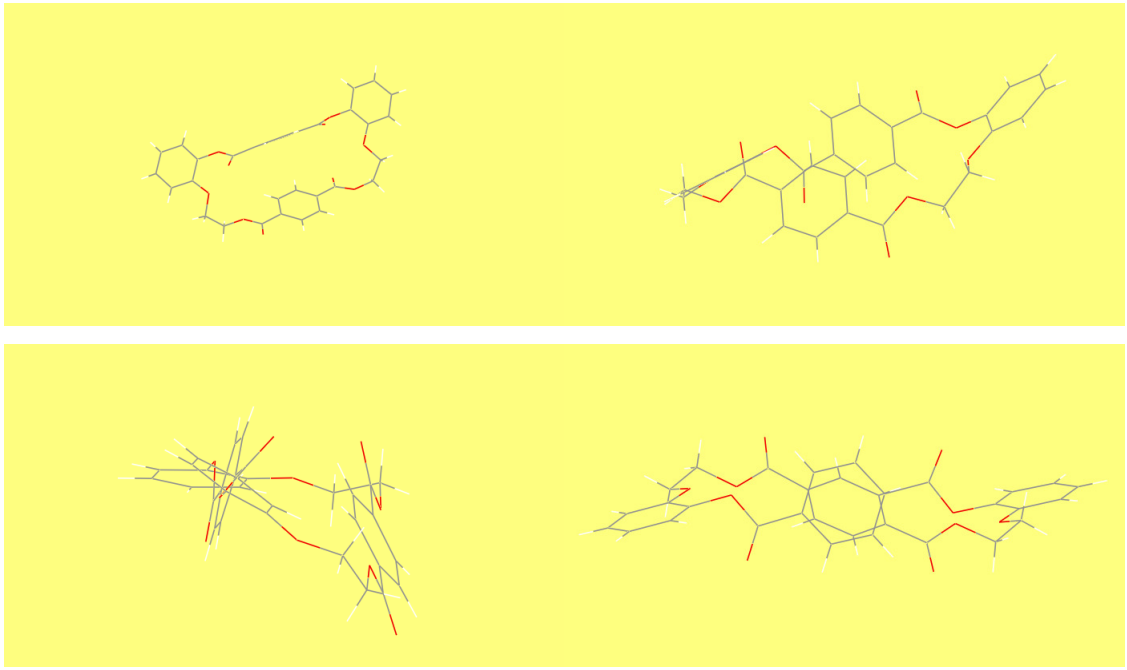


Figure 49: X-Ray crystal structure of **353** *from various aspects*

Compound **353** contains four phenyl rings. These rings and the carbonyl groups deform the structure, severely restricting the flexibility commonly recognized for crown ethers. The structure takes on the form of a flattened and slightly deformed ellipsoid. (cf. **352**)

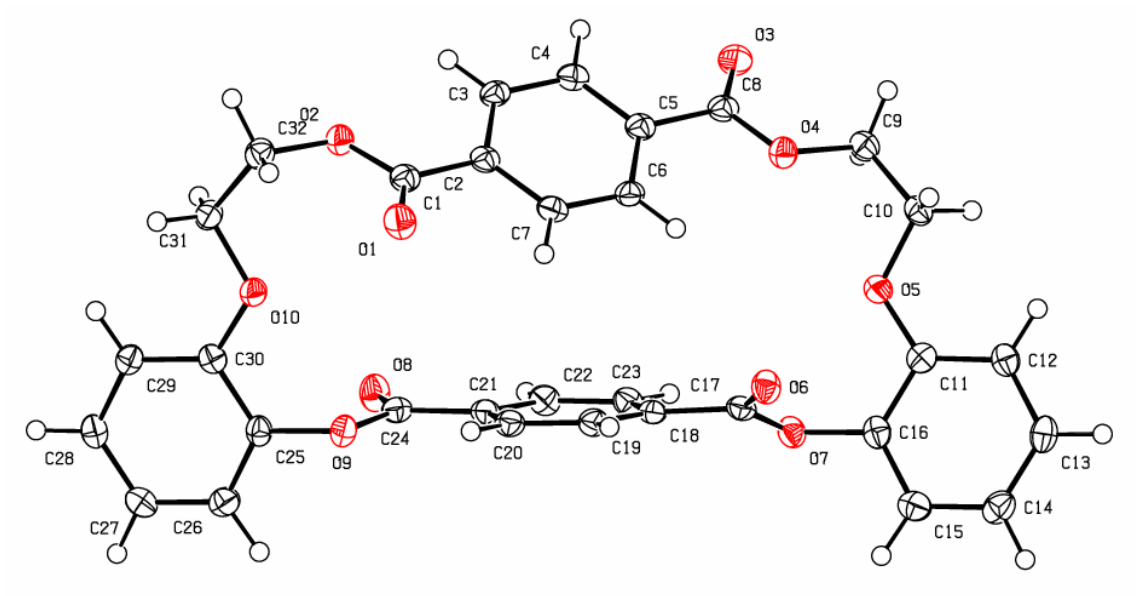


Figure 50: X-Ray crystal structure of **353**

Bond lengths		Estimated standard deviation
C(25)–C(30)	1.393 Å	2
C(16)-C(11)	1.398 Å	2
O(5)-C(10)	1.4291 Å	18
O(10)–C(31)	1.4320 Å	18
C(17)-C(18)	1.488 Å	2
C(21)-C(24)	1.491 Å	2
Bond angles		**Estimated standard deviation**
C(11)–C(16)–O(7)	119.39°	13
C(30)–C(25)–O(9)	118.79°	13
O(10)–C(31)–C(32)	107.89°	12
C(2)–C(1)–O(2)	112.52°	13
C(16)–C(11)–O(5)	116.26°	13
O(4)–C(9)–C(10)	107.68°	12
Torsion angles		**Estimated standard deviation**
O(5)–C(11)–C(16)–O(7)	–0.8°	2
O(9)–C(25)–C(30)–O(10)	1.06°	19
O(3)–C(8)–O(4)–C(9)	–6.0°	2
C(32)–O(2)–C(1)–O(1)	–0.1°	2
C(5)–C(8)–O(4)–C(9)	173.56	12
O(6)–C(17)–C(18)–C(23)	152.02	15
C(20)–C(21)–C(24)–O(8)	173.36	15
O(10)–C(31)–C(32)–O(2)	60.52	17
C(5)–C(8)–O(4)–C(9)	173.56	12
O(4)–C(9)–C(10)–O(5)	53.87	16

Table 8: Representative bond lengths, bond angles and torsion angles of 353.

Macrocycle **353** crystallizes in the monoclinic space group $P2_1/c$ with four independent molecules per asymmetric unit. The bond length for C(25)–C(30) is 1.393 Å and for C(16)-C(11) is 1.398 Å. Bonds O(5)–C(10) and O(10)–C(31) are almost the same distances at 1.4291 Å and 1.4320 Å respectively. The angle for C(11)–C(16)–O(7) is 119.39° and is close to the C(30)–C(25)–O(9) angle of 118.79°. However, torsion angles for O(5)–C(11)–C(16)–O(7) and O(9)–C(25)–C(30)–O(10) are –0.8° and 1.06° respectively. This gives an indication that the compound is not completely symmetrical in the solid state as although the similar bond on each side of the crystal have very similar bond lengths and angles, as expected, they differ in torsion angle which would no be expected for a symmetrical molecule. Also demonstrating the asymmetrical nature of the crystal structure is the comparison between torsion angle values associated with the terephthalate unit are similar and equal –6.0° for O(3)–C(8)–O(4)–

C(9) and –0.1° for C(32)–O(2)–C(1)–O(1), although the bond angles and lengths are similar to each other.

From - To	Distance (Å)
O1 – O7	7.7
O1 – O10	3.1
O4 – O8	7.6
C8 – C20	3.5
O2 – O9	4.5
O4 – O7	4.7
O4 – O9	8.4
O5 – O10	10.1
C10 – C30	11.7

Table 9: Dimensions of the cavity of **353**.

Table 9 above shows some distances indicating the size of the cavity of macrocycle **353**.

2.9.3: Discussion of the X-ray crystal structure of **363**

Crystals suitable for single crystal X-ray crystallographic determination of **363** were grown by slow evaporation from chloroform:hexane (1:3), yielding colourless block shaped crystals.

Selected bond distances, torsion angles and angles of non-hydrogen atoms are given in table 10. Table 11 gives selected measurements across the cavity of the macrocycle which are illustrative of the cavity size. Figure 51 shows perspective views of the crystal structure and figure 52 shows the crystal structure with the atomic numbering.

Figure 51: X-Ray crystal structure of **363** *from various aspects*

363 contains a ten membered ring with seven carbon and 3 oxygen atoms and one phenyl ring. The phenyl ring and the carbonyl groups restrict the flexibility commonly seen in crown ethers causing deformation of the structure. The ten membered ring takes on the form of a flattened and slightly deformed ellipsoid.

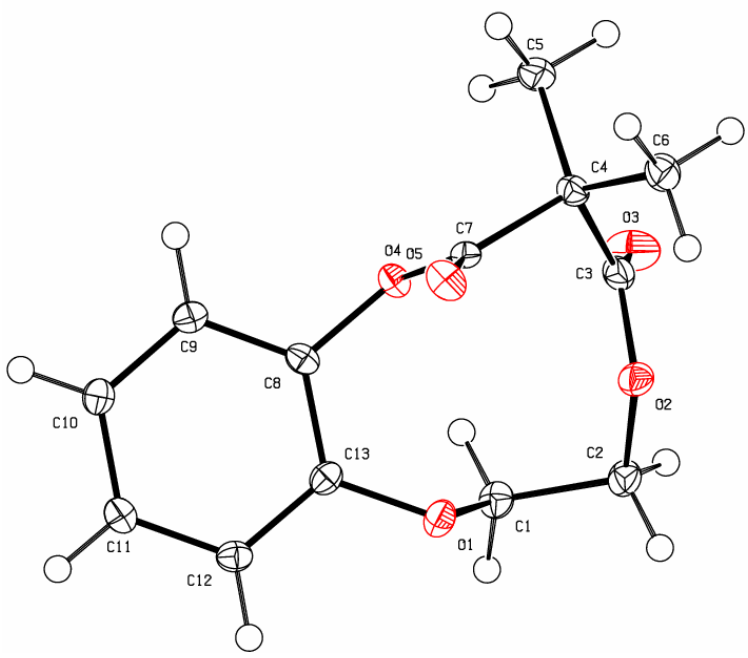


Figure 52: X-Ray crystal structure of **363**

Bond lengths		Estimated standard deviation
O(3)–C(3)	1.198 Å	3
C(7)–O(5)	1.185 Å	2
C(1)–C(2)	1.514 Å	3
C(8)–C(13)	1.397 Å	3
C(3)–C(4)	1.529 Å	3
C(4)–C(5)	1.532 Å	3
Bond angles		**Estimated standard deviation**
C(3)–O(2)–C(2)	116.69°	16
C(7)–O(4)–C(8)	118.17°	15
C(13)–C(8)–O(4)	118.63°	16
C(6)–C(4)–C(5)	110.95°	16
C(3)–C(4)–C(7)	103.17°	15
O(5)–C(7)–O(4)	124.44°	17
Torsion angles		**Estimated standard deviation**
C(2)–O(2)–C(3)–O(3)	–25.6°	3
O(5)–C(7)–O(4)–C(8)	–11.3°	3
C(13)–O(1)–C(1)–C(2)	146.37°	16
C(3)–C(4)–C(7)–O(4)	–53.89°	18
O(4)-C(8)-C(13)-O(1)	8.6°	3
O(4)–C(8)–C(9)–C(10)	175.31°	18
C(11)–C(12)–C(13)–O(1)	176.71°	18
C(9)-C(10)-C(11)-C(12)	0.7°	3
C(9)-C(8)-C(13)-C(12)	0.6°	3

Table 10*: Representative bond lengths, bond angles and torsion angles of* **363***.*

Macrocycle **363** crystallizes in the monoclinic space group $P2_1$ with four independent molecules per asymmetric unit. The bond length for C(1)–C(2) is 1.514 Å and for C(8)–C(13) is 1.397 Å. Bonds O(3)–C(3) and C(7)–O(5) are almost the same distances at 1.198 Å and 1.185 Å respectively. The angle for C(3)–O(2)–C(2) is 116.69° and is close to the C(7)–O(4)–C(8) angle of 118.17°. Each of these differences is to be expected because of the hybridisation of the atoms involved in the bonds and the differences between the aromatic and alkyl carbons. The aromatic ring and hence it's substituents are non-planar as demonstrated by the torsion angles of O(4)-C(8)-C(13)-O(1), C(9)-C(8)-C(13)-C(12) and O(4)–C(8)–C(9)–C(10), this is caused by the stress from the larger 10 membered ring.

From – To	Distance (Å)
O1 – O2	2.8
O1 – O4	2.8
O2 – O4	3.0
C2 – C8	4.0
C1 – C4	4.0
C4 – C13	4.3

Table 11: Dimensions of the cavity of **363**

2.9.4: Discussion of the X-ray crystal structure of 343

Crystals suitable for single crystal X-ray crystallographic determination of **352** were grown by slow evaporation from chloroform:hexane (1:2), yielding colourless needle shaped crystals.

Selected bond distances, torsion angles and angles of non-hydrogen atoms are given in table 12. Figure 53 shows perspective views of the crystal structure and figure 54 shows the crystal structure with atomic numbering.

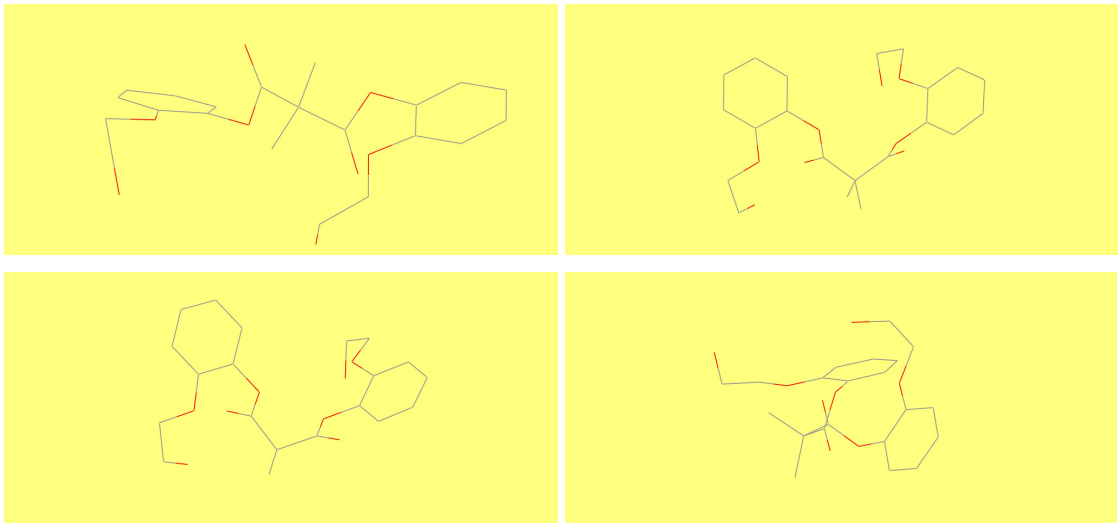


Figure 53: X-Ray crystal structure of **343** *from various aspects*

343 was synthesised as a precursor to macrocycle **357** and as such is different from each of the other crystal structures as they are each macrocycles and have a ring. **343** is a branched molecule with the main chain containing seventeen atoms.

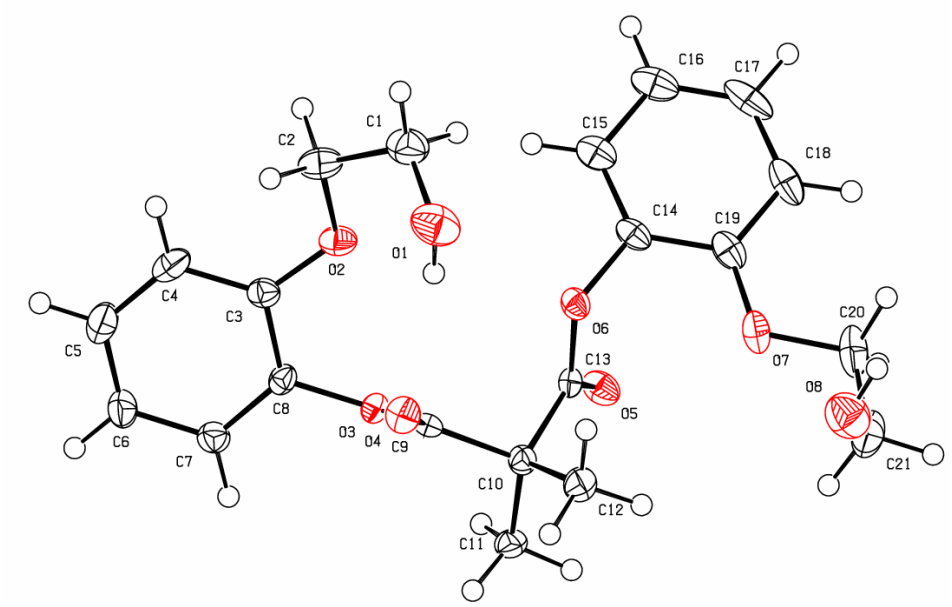


Figure 54: X-Ray crystal structure of **343** *with atomic numbering*

Bond lengths		**Estimated standard deviation**
C(20)–C(21)	1.496 Å	3
C(14)–O(6)	1.409 Å	2
C(1)–C(2)	1.481 Å	3
C(8)–O(3)	1.412 Å	2
C(3)–C(8)	1.388 Å	3
C(10)–C(12)	1.529 Å	3
Bond angles		**Estimated standard deviation**
C(3)–O(2)–C(2)	116.9°	1
C(20)–O(7)–C(19)	118.6°	1
C(1)–C(2)–O(2)	105.8°	2
C(11)–C(10)–C(12)	111.5°	2
C(9)–C(10)–C(13)	108.3°	1
C(15)–C(16)–C(17)	119.6°	2
Torsion angles		**Estimated standard deviation**
C(21)–C(20)–O(7)–C(19)	–167.9°	2
C(1)–C(2)–O(2)–C(3)	–154.9°	2
O(3)–C(9)–C(10)–C(13)	–65.0°	2
C(19)–C(14)–O(6)–C(13)	69.8°	2
C(15)–C(16)–C(17)–C(18)	–2.8°	3
C(4)–C(5)–C(6)–C(7)	–0.5°	3

Table 12*: Representative bond lengths, bond angles and torsion angles of* **343**.

Compound **343** crystallizes in the monoclinic space group $Pna2_1$ with four independent molecules per asymmetric unit. Each of the bond lengths and angles are within normal levels and there are no significant differences between similar bonds in varying locations within the crystal. However, there are variations of torsion angles for similar groups across the crystal; examples include C(1)–C(2)–O(2)–C(3) and C(21)–C(20)–

O(7)–C(19) with angles of –154.9° and –167.9° respectively and the two aromatic rings are also none planar with torsion angles of –2.8° and –0.5° measured across C(15)–C(16)–C(17)–C(18) and C(4)–C(5)–C(6)–C(7) respectively. The aromatic ring containing C(15)–C(16)–C(17)–C(18) has the lager torsion angle indicating that it is under more strain than the other aromatic ring in the crystal. Although the most favourable torsion angle for an alkyl chain is ±60°, ±120° or 180° for steric reasons, with the ideal situation giving a torsion angle of 180° between the two largest groups at either end of a chain. So in the case of C(1)–C(2)–O(2)–C(3) or C(21)–C(20)–O(7)–C(19) the most favourable torsion angle is 180°, therefore C(1)–C(2)–O(2)–C(3) is under increased strain with the C(1)-C(2) bond being at 154.9° in the anticlockwise direction to O(2)-C(3) bond.

With the crystal of **343** each molecule is hydrogen bonded to two separate molecules through the hydroxy groups containing the oxygen atoms O1 and O8. O1 acts as a hydrogen bond acceptor and H8 (the hydrogen atom on O8) acts as a hydrogen bond donor, the bond length is 2.043Å. These hydrogen bonds are depicted in figure 55 below.

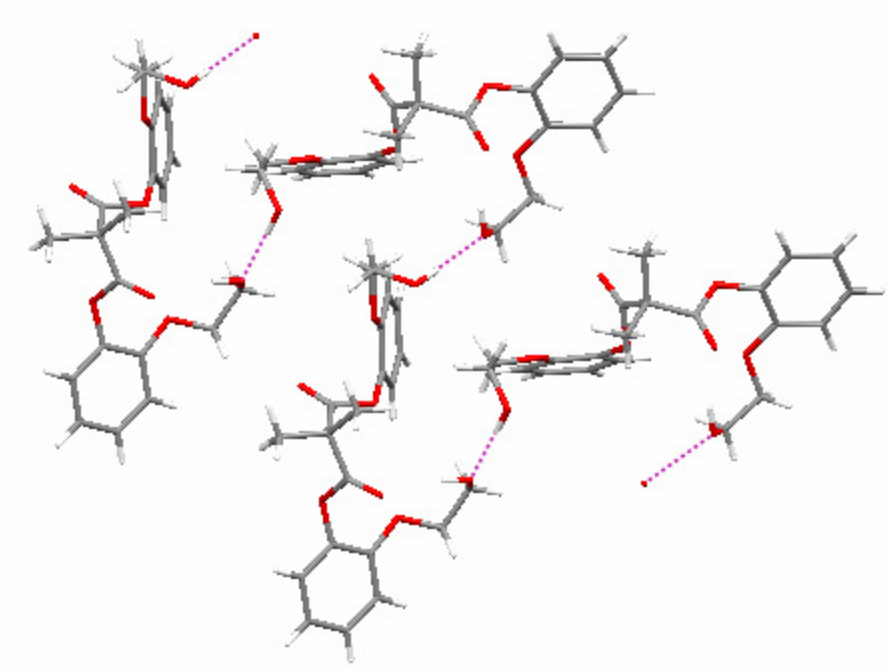


Figure 55: X-ray crystal structure of **343** *depicting the hydrogen bond interactions*

2.10: Differentiation between Structural Isomers:

In this section of the thesis the differentiation of the isomers is discussed. This differentiation is very important for two reasons. Firstly, so the correct isomers are identified and thus the data reported within this thesis is correct; and secondly because one pair of isomers, **343** and **346** are biologically active and if work is to continue using **343** and **346** to develop compounds with higher activity then it is of utmost importance to unambiguously identify the different isomers.

2.10.1: Differentiation between Structural Isomers 343 *and* 346:

The structures of **343** and **346** (figure 56) show that these two compounds are isomers and it is possible under the right conditions that there could be an intermolecular transesterification reaction transforming one product into the other.

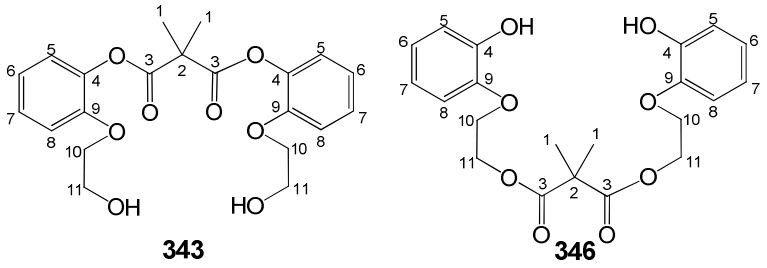
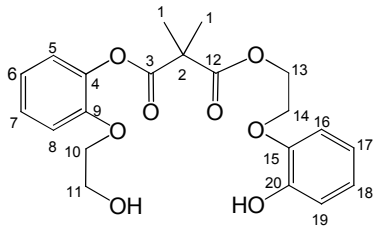


Figure 56: Side by side comparison of **343** *and* **346**.

Although the phenol in the starting material, 2-(2-hydroxyethoxy)phenol, should be more reactive than the aliphatic alcohol this will invariably mean that the less reactive aliphatic alcohol will form the more stable product. The method of synthesis of both **343** and **346** is based on the reactivity of the phenol compared to aliphatic alcohol. On the addition of one equivalent of dimethyl malonyl dichloride to two equivalents of 2-(2-hydroxyethoxy)phenol then the first product to form is expected be **343** because the phenol is more reactive than the aliphatic alcohol. However, the diacid dichloride may also react with the aliphatic alcohol to form **346**. According to Cheruvallath *et al*.[67] fast mechanical stirring and slow addition of the diacid dichloride is the most important factor for determining the product of the reaction, although acetic anhydride was added to form the ester instead of dimethyl malonyl dichloride.

Also it is possible to get intermolecular transesterification. This process would lead to **343** and **346** being interchangeable, but most notable would also lead to the creation of new product **364** as shown in figure 57 below.



364

Figure 57: Structure of **364**

For transesterification to occur the new ester bond formed should be more stable than the original ester bond. In the case of **364** and **346** they are both more stable than **343** so the possibility exists for this intermolecular transesterification to occur. In the plethora of published transesterification reactions a catalyst (acid and base) is used. Some of the more alkali catalysts for this reaction are metal hydroxides, carbonates and metal alkoxides, sulphuric, sulphonic or hydrochloric acids are the most commonly used acid catalysts.[68] The alkali catalysts are most commonly used because there is a faster reaction time and moderate conditions can be used, with typical reaction temperatures of 60 ^{o}C to 70 ^{o}C. Although temperatures for acidic catalysed transesterification are typically less, 55 ^{o}C to 80 ^{o}C, the acid catalysts is typically a strong acid.

For the synthesis of **343** mild basic conditions were used, with the addition of triethylamine to react with the hydrogen chloride produced as a by-product of the reaction. This may act as a catalyst for the transesterification reaction, either as the free base or as the conjugate acid, although this is not likely to a great extent with the highest temperature being used for this reaction being room temperature.

For the synthesis of **346** both alkali and acidic conditions were used, depending on the stage of the synthesis (basic conditions for esterification step and acidic conditions for the deprotection step). Although this may increase the likelihood of the transesterification reaction occurring the difference in the NMR, both ^{1}H and ^{13}C, to that of the **343** strongly indicates that the structure is different from that of **343**. Table 13 below shows the actual versus predicted ^{1}H and ^{13}C NMR of **343** and **346**. Predictions were carried out using ChemBioDraw Ultra Version 11.0.1 © 1986-2007 CambridgeSoft.

One of the clear differences between **343** and **346** is the presence of two phenol groups in **346** and none in **343**, this has a basic wet chemistry test which shows the presence of a phenol and not of an aliphatic alcohol. This test is the addition of aqueous iron(III)

chloride to a solution of the compound being tested. Using this test **343** gave negative results for the presence on a phenol, the iron(III) chloride solution staying yellow. The same test gave a positive result for the presence of phenol on **346**, with the iron(III) chloride solution turning purple on contact with the solution of **346**.

The most compelling evidence that **343** was successfully isolated and identified is the X-ray crystal structure. The X-ray structure is discussed in section 2.9.4. This structure agrees with the NMR assignments made for **343**. Figures 58 and 59 below show the proton NMR spectra of **343** and **346** respectively.

Atom Number	**343** ^{1}H Actual (Predicted)	**346** ^{1}H Actual (Predicted)	**343** ^{13}C Actual (Predicted)	**346** ^{13}C Actual (Predicted)	**364** Predicted ^{1}H (^{13}C)
1	1.71(1.37)	1.67(1.47)	23.19(22.8)	22.08(22.8)	1.42(22.8)
2			50.45(50.0)	49.36(50.8)	(50.4)
3			170.90(172.1)	169.91(171.1)	(172.1)
4			139.63(142.0)	149.06(148.8)	(142.0)
5	7.15(7.18)	6.86-6.82(6.84)	121.18(120.6)	120.07(116.5)	7.18(120.6)
6	6.88-6.92 (6.98)	7.08(6.84)	122.44(120.7)	121.35(121.7)	6.98(120.7)
7	7.02(7.15)	6.86-6.82(6.90)	127.33(126.1)	126.28(121.9)	7.15(126.1)
8	6.88-6.92 (6.96)	6.98(6.82)	113.6(114.8)	112.58(115.8)	6.96(114.8)
9			150.11(153.9)	138.54(145.6)	(153.9)
10	4.04(4.33)	3.94(4.42)	70.29(69.5)	69.14(66.7)	4.33(69.5)
11	3.71(3.70)	3.64(4.45)	61.03(60.9)	59.87(62.6)	3.69(60.9)
12					(171.1)
13					4.45(62.6)
14					4.42(66.7)
15					(145.6)
16					6.82(115.8)
17					6.90(121.1)
18					6.84(121.7)
19					6.84(116.5)
20					(148.8)

Table 13: Actual versus predicted ^{1}H and ^{13}C NMR of **343, 346** *and predicted NMR values of* **364**.

At no stage of the synthesis was a product isolated whose NMR matched (or nearly matched) the predicted values for **364** in the table above

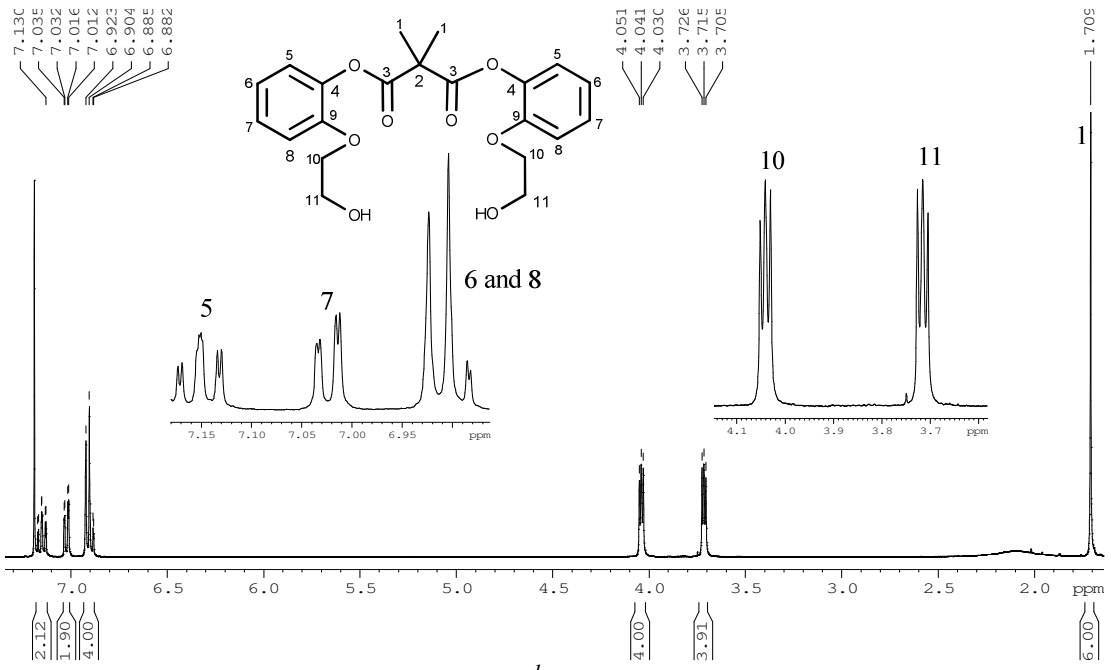


Figure 58: [1]H NMR of **343**.

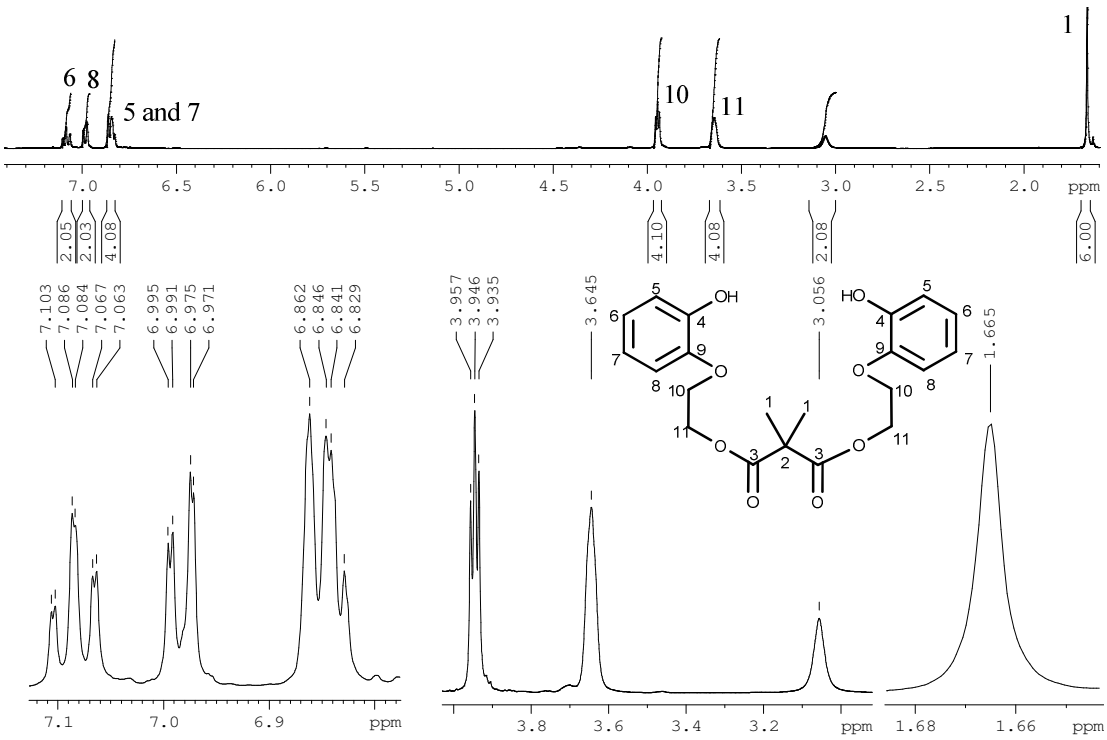


Figure 59: [1]H NMR of **346**.

Shown in figures 58 and 59 are the ^{1}H NMR spectra of **343** and **346,** which are clearly spectra of different compounds. The singlets for the methyl groups, H1 on both structures in figure 56 above, are different by 0.04 ppm, also each of the peaks for the CH_2 groups, H's 10 and 11, are different, as are the peaks in the aromatic region. The sum of these differences is a clear indicator that the two compounds are different from each other. Together with the X-ray of **343** we submit this is strong evidence of the

correct assignment of **343** and **346**. Also the peaks for H's 10 and 11 on **343** closely match that of the same group in 2-(2-hydroxyethoxy)phenyl acetate reported by Cheruvallath *et al.*[67] The ^{13}C NMR of each of these compounds is different, as shown below in figures 60 and 61.

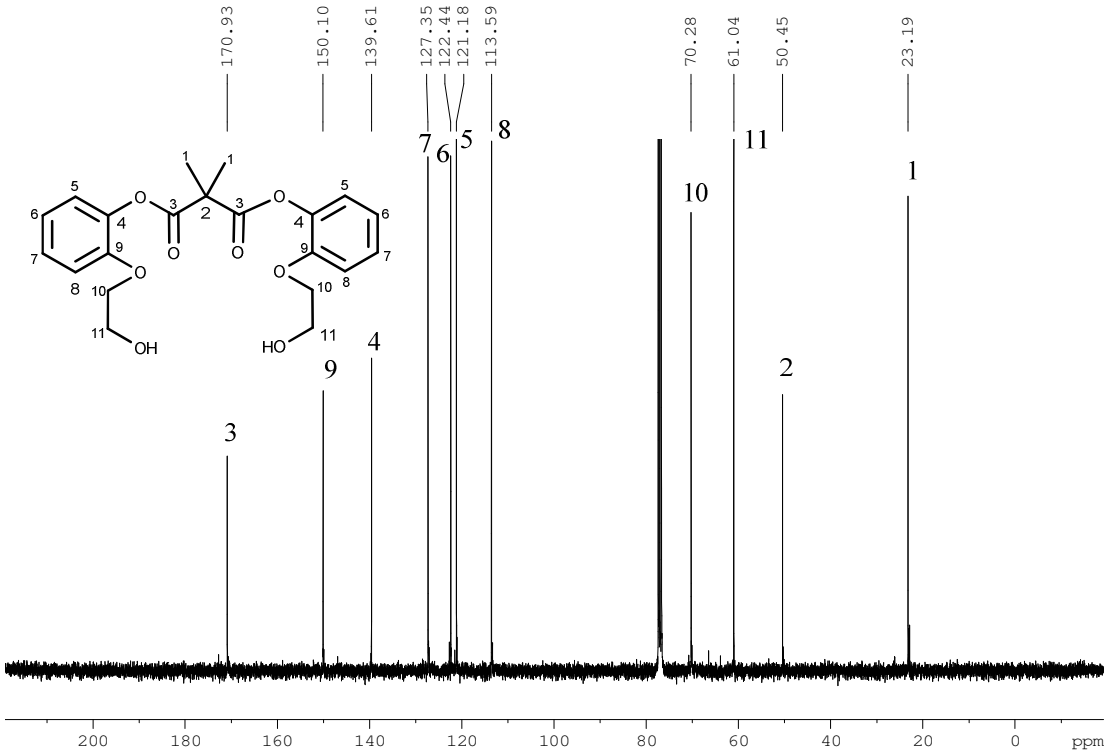


Figure 60: ^{13}C NMR of **343**.

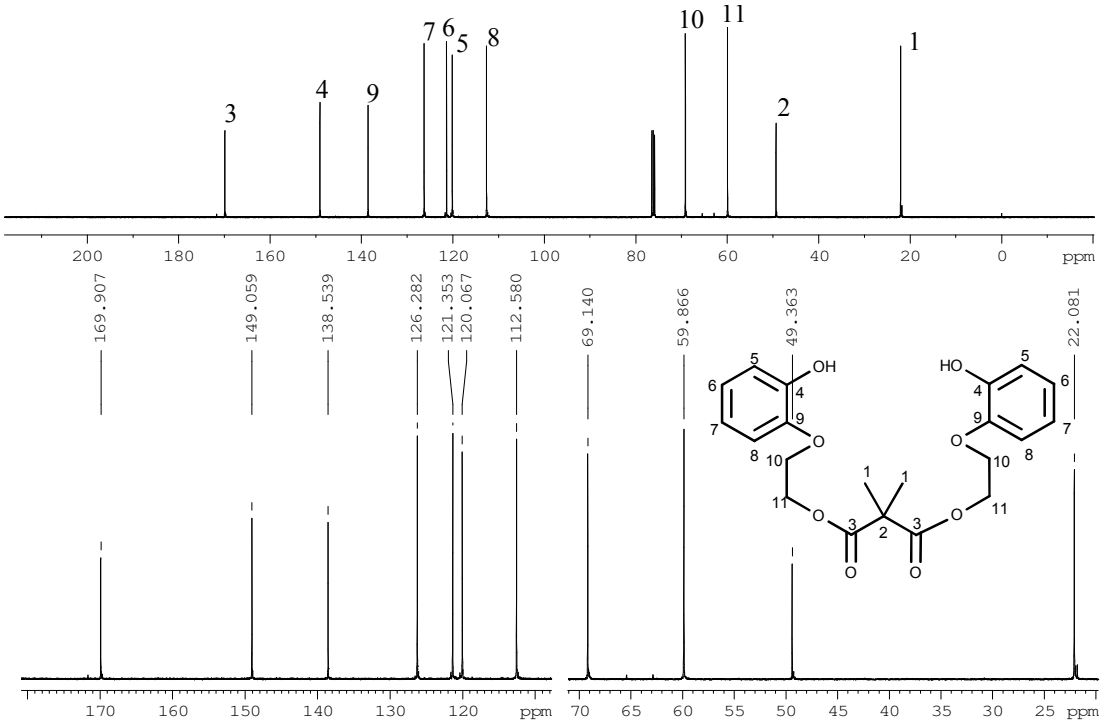


Figure 61: ^{13}C NMR of **346**

Seen in figure 60 and 61 above the ^{13}C NMR spectra of **343** and **346** are clearly of different spectra showing that they are also significantly different compounds, the peaks for the methyl groups, C1 of **343** is at 23.19 ppm and is at 22.08 ppm for C1 of **346**. For C2 they are at 50.45 ppm and 49.26 ppm respectively. Each of the other peaks also differ across the spectrum. The sum of all these differences, ^{1}H NMR, ^{13}C NMR, the iron(III) chloride wet chemistry test and X-ray crystallography provides clear evidence that both **343** and **346** have been synthesised and correctly identified.

2.10.2: Differentiation between Structural Isomers **339** *and* **355:**

339 and **355** (figure 62) are isomers and it is possible under the right conditions that there could be an intermolecular transesterification reaction transforming one product into the other.

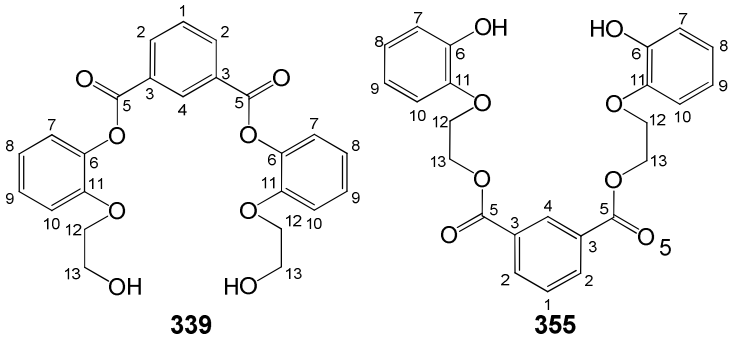


Figure 62: Side by side comparison of **339** *and* **355**.

The arguments for and against the possibility of the transesterification reaction occurring have been made in section 2.10.1, as such these arguments will be referred to when evaluating the evidence dividing to establish that **339** and **355** have been correctly synthesised and identified.

The intermolecular transesterification would lead to **339** and **355** being interchangeable, but most notably would also lead to the creation of new product **365** as shown in figure 63 below.

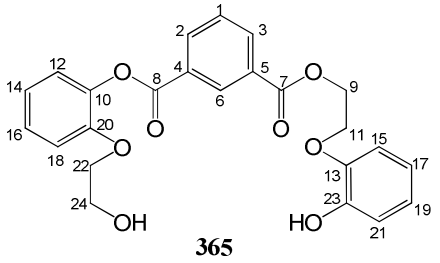


Figure 63: Structure of **365**

The first test to be discussed here is the wet chemistry test using iron(III) chloride to test for the presence for the phenol groups. In this case compound **339** tested negative for the presence of the phenol with the iron(III) chloride solution remaining yellow and **355** tested positive with the iron(III) chloride solution turning purple.

The ^{1}H and ^{13}C NMR spectra for **339** and **355** are shown in the figures 64 to 67 below. Below these figures in table 14 are a list of the actual versus predicted ^{1}H and ^{13}C NMR of **339** and **355** and the predicted peaks for **365**. Predictions were carried out using ChemBioDraw Ultra Version 11.0.1 © 1986-2007 CambridgeSoft.

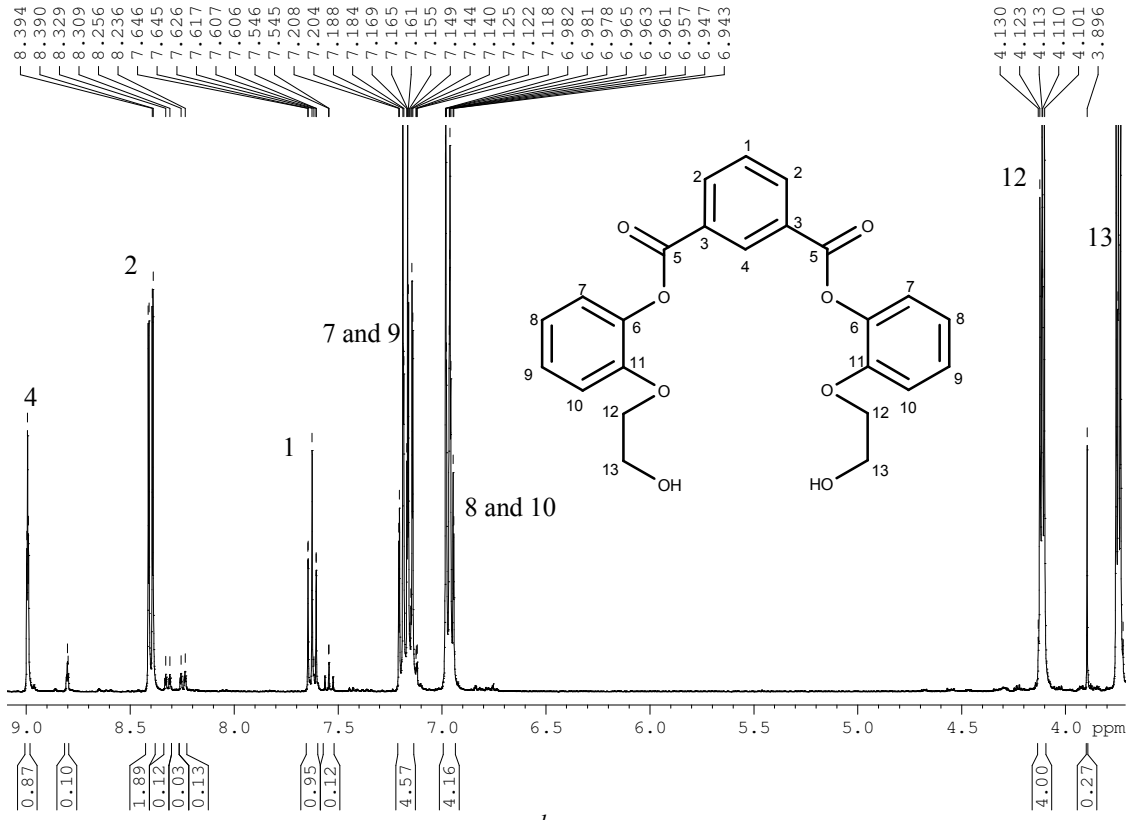


Figure 64: ^{1}H NMR of **339**

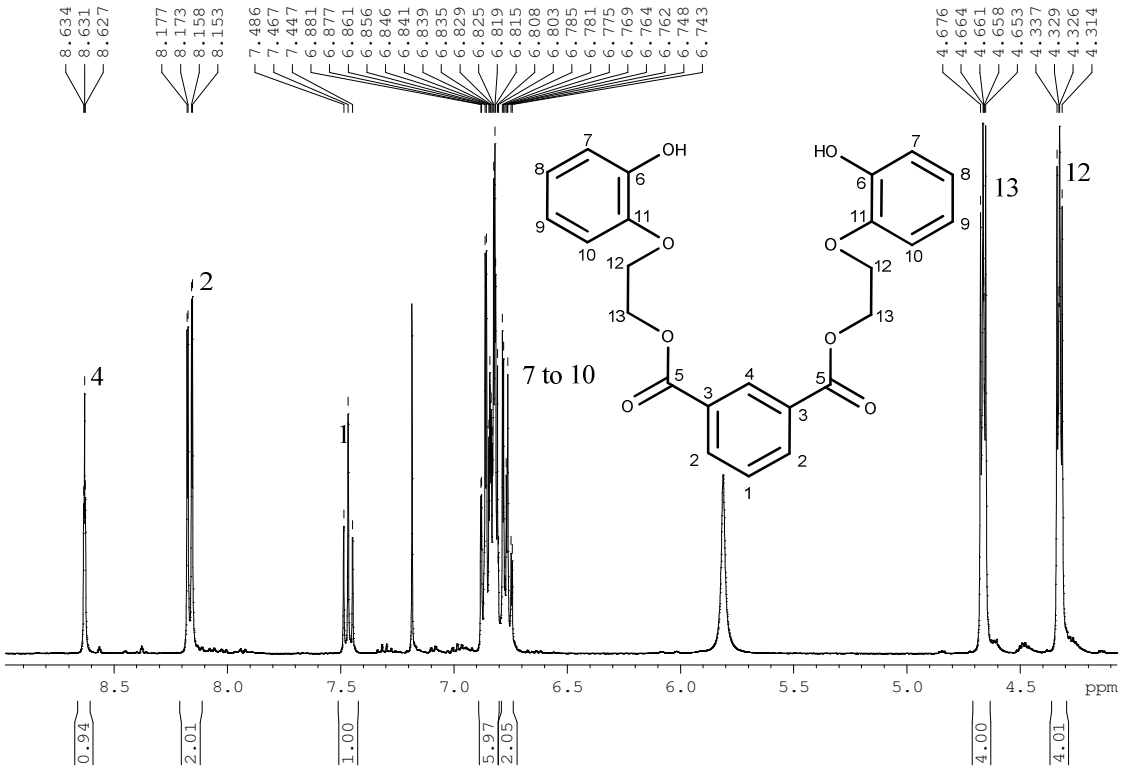


Figure 65: ^{1}H NMR of **355**

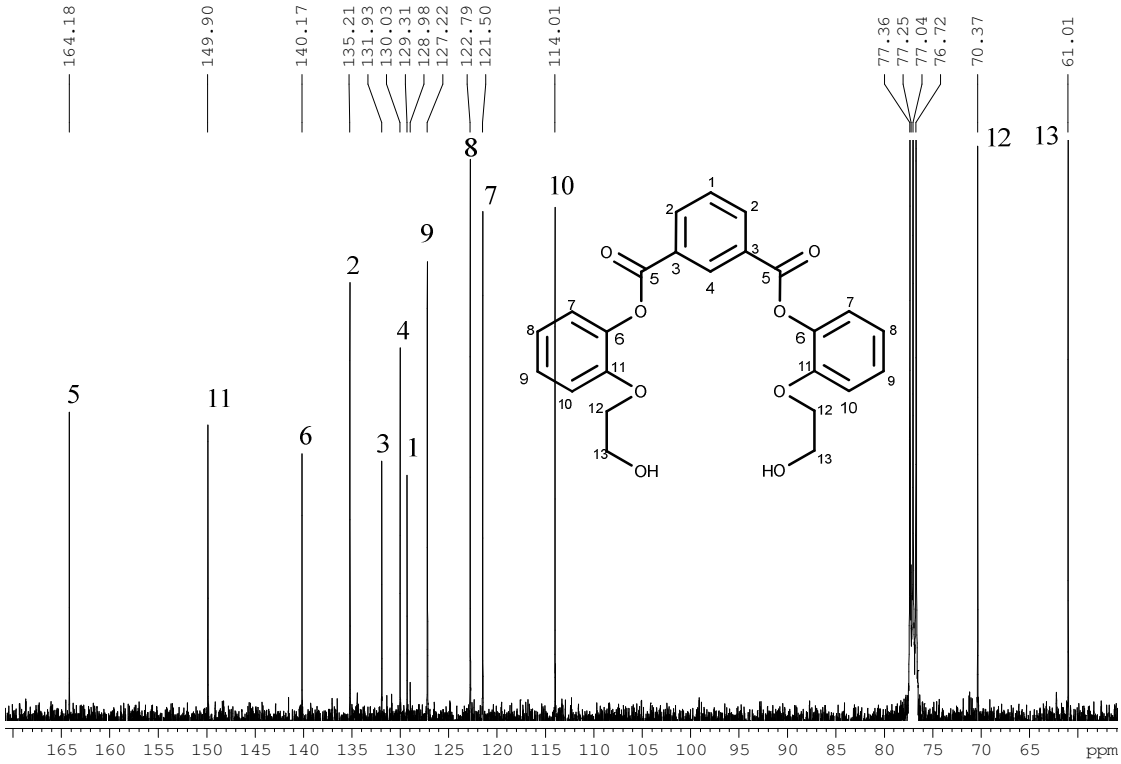


Figure 66: ^{13}C NMR of **339**

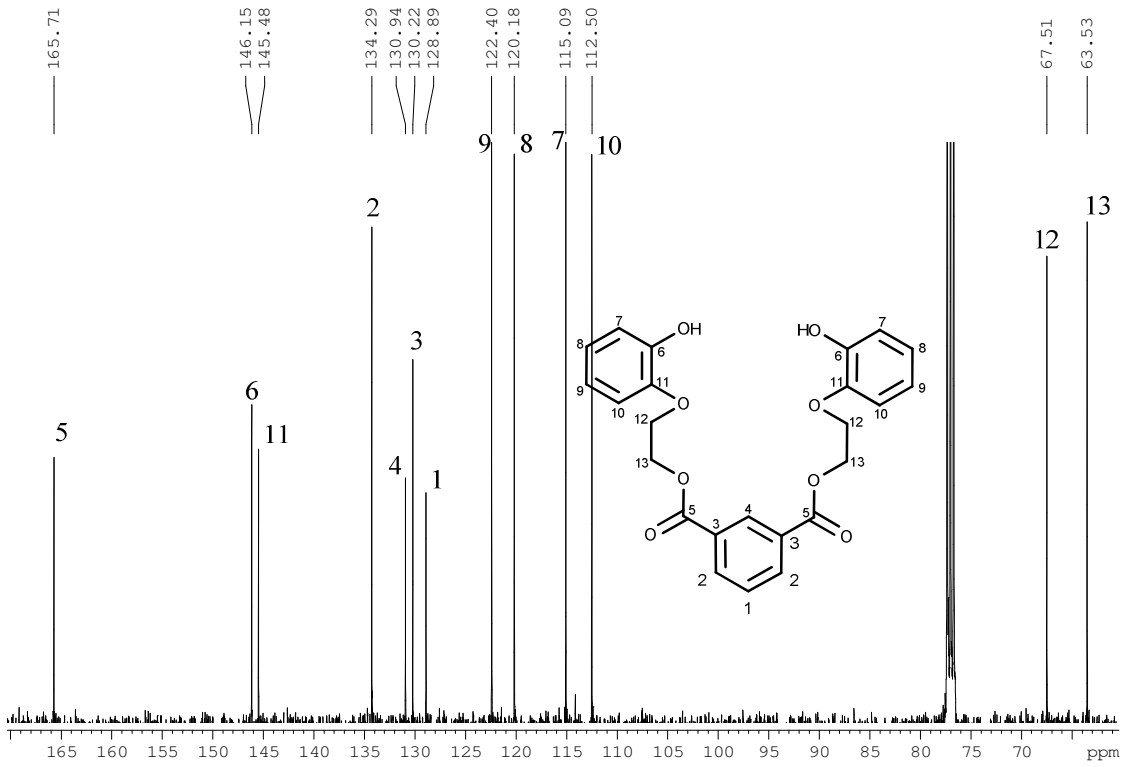


Figure 67: ^{13}C NMR of **355**

Atom Number	**339** ^{1}H Actual (Predicted)	**355** ^{1}H Actual (Predicted)	**339** ^{13}C Actual (Predicted)	**355** ^{13}C Actual (Predicted)	**366** Predicted ^{1}H (^{13}C)
1	7.62(7.64)	7.46(7.56)	129.31(128.5)	128.89(128.5)	7.60(128.5)
2	8.40(8.47)	8.16(8.26)	135.21(135.5)	134.29(134.2)	8.43(134.6)
3			131.93(130.1)	130.22(131.1)	8.30(135.1)
4	8.99(8.62)	8.63(8.28)	130.03(130.6)	130.94(129.8)	(130.1)
5			164.18(166.3)	166.71(166.9)	(131.1)
6			140.17(138.5)	146.15(148.8)	8.45(130.2)
7	7.12-7.21 (7.26)	6.74-6.88 (6.84)	121.50(120.6)	115.09(116.5)	(166.9)
8	6.98-6.94 (7.08)	6.74-6.88 (6.84)	122.79(120.7)	120.18(121.7)	(166.2)
9	7.12-7.21 (7.24)	6.74-6.88 (6.90)	127.22(126.1)	122.40(121.9)	4.62(63.9)
10	6.98-6.94 (7.06)	6.74-6.88 (6.82)	114.01(114.8)	112.50(115.8)	(138.5)
11			149.90(153.9)	145.48(145.6)	4.60(66.7)
12	4.12(4.33)	4.32(4.60)	70.37(69.5)	67.51(66.7)	7.26(120.6)
13	3.75(3.69)	4.66(4.62)	61.01(60.9)	63.53(63.7)	(145.6)
14					7.08(120.7)
15					6.82(115.8)
16					7.24(126.1)
17					6.90(121.9)
18					7.06(114.8)
19					6.84(121.7)
20					(153.9)
21					6.84(116.5)
22					4.63(69.5)
23					(148.8)
24					3.69(60.9)

Table 14: Actual versus predicted ^{1}H and ^{13}C NMR of **339, 355** *and predicted NMR values of* **366**

In the case of **339** the predicted ^{1}H-NMR closely matches the actual data recorded for the hydrogens on the two aliphatic carbons, H's 12 and 13. Although it is not an exact

match it is in the correct area and more importantly is significantly different from that of the equivalent hydrogens on **355**, H's 12 and 13. One other significantly different hydrogen from these isomers is H4. In **339** H4 is ortho to two ester groups, each synthesised from a phenol; H4 in **355** is ortho to two ester groups, each synthesised from an aliphatic alcohol. H4 is predicted to be further downfield in the NMR spectrum of **339** than in the NMR spectrum of **355** due to the effects of the phenolic esters and of the aliphatic esters. Although in each spectra H4 appears further downfield than predicted it is clear in the spectrum of **339** that H4 is significantly further downfield than in the spectrum of **355**. Hydrogens H12, H13 and H14 are the most significant hydrogens for differentiating the two structures by NMR, as they are the hydrogens that will change most significantly between the isomers.

The ^{13}C NMR spectra of these two compounds are also significantly different, with the NMR of **339** more closely matching the predicted values for many of the carbons. Also it must be noted that again none of the intermediate product **366** was isolated.

Also to be taken into account here is the macrocycle **352**, page 55, which has been synthesised using **339** as a starting material. Compound **339** was dissolved in dichloromethane and then triethylamine was added before being linked between the aliphatic alcohols using terephthaloyl dichloride. Further to this is that **352** was made using the one pot method in with 2-(2-hydroxyethoxy)phenol was first linked using the isophthaloyl dichloride to form the intermediate and then extra base (triethylamine) added before the addition of terephthaloyl dichloride to form the macrocycle. The structure of this macrocycle has been proven by X-ray crystallography, and confirms that **339** must have been formed in both methodologies in order to obtain **352** as the product. The fact that this macrocycle has formed and not the isomer, **358**, shows that not only did **339** from but was also stable to the extra base present.

When the NMR data is taken into account, with the wet chemistry test and the X-ray of macrocycle **352** and the fact that the same methodology was used in the synthesis of these compounds as was used in **343** and **346** it has been proven that compounds **339** and **355** have been successfully isolated and correctly identified.

2.10.3: Differentiation between Structural Isomers **342** *and* **356:**

342 and **356** (figure 68) are isomers and it is possible under the right conditions that there could be an intermolecular transesterification reaction transforming one product into the other.

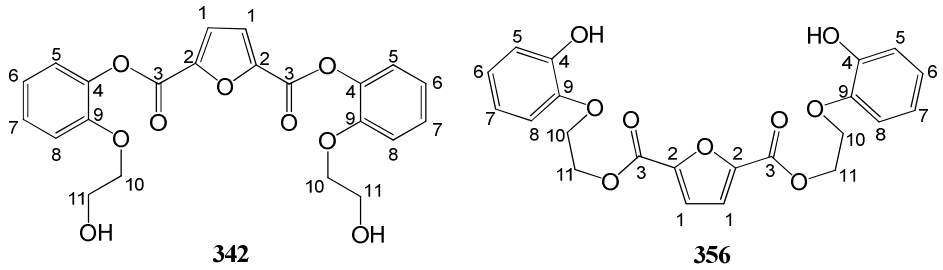


Figure 68: Comparison of **342** *and* **356**

The arguments for and against the possibility of the transesterification reaction occurring have been made in section 2.10.1, as such these arguments will be referred to when evaluating the evidence to establish that **342** and **356** have been correctly synthesised and identified.

As before, sections 2.10.1 and 2.20.2, it is possible to get intermolecular transesterification but this process would lead to **342** and **356** being interchangeable, but most notably would also lead to the creation of new product **366** as shown in figure 69 below.

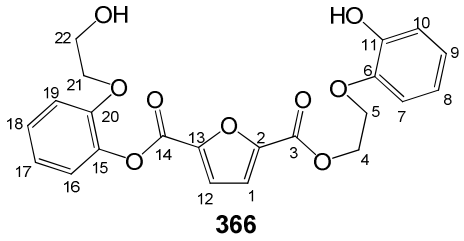


Figure 69: Structure of **366**

The first test to be discussed here is the wet chemistry test using iron(III) chloride to test for the presence for the phenol groups. In this case compound **342** tested negative for the presence of the phenol with the iron(III) chloride solution remaining yellow and **356** tested positive with the iron(III) chloride solution turning purple.

The ^{1}H and ^{13}C NMR spectra for **342** and **356** are shown in the figures 70 to 73 below. Below these figures in table 15 are a list of the actual versus predicted ^{1}H and ^{13}C NMR of **342** and **356** and the predicted peaks for **366**. Predictions were carried out using ChemBioDraw Ultra Version 11.0.1 © 1986-2007 CambridgeSoft.

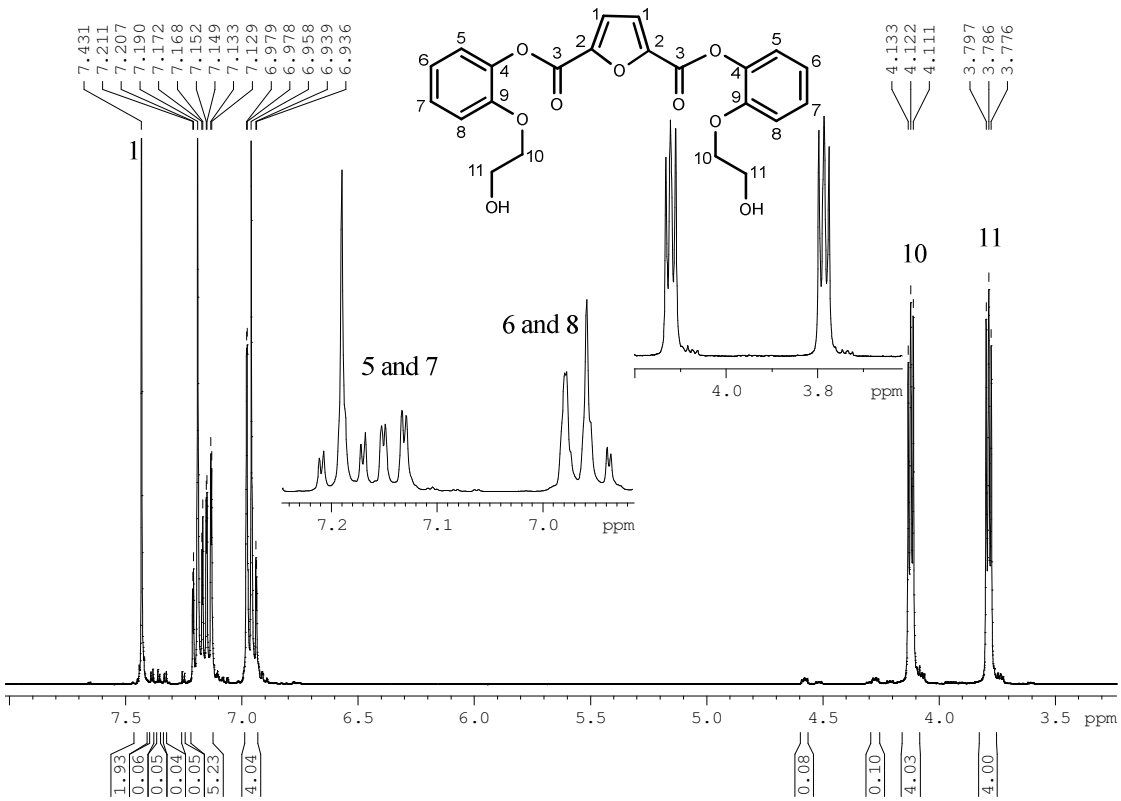


Figure 70: [1]H NMR of **342**

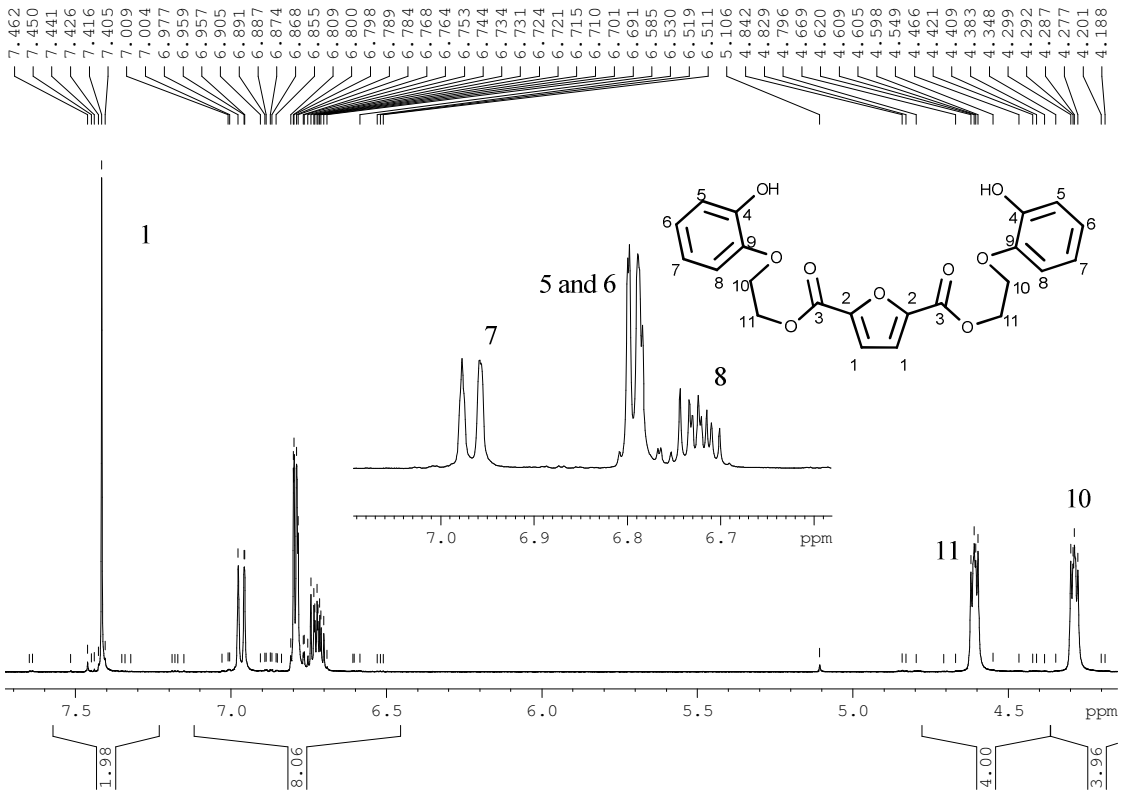


Figure 71: [1]H NMR of **356**

Figure 72: ^{13}C NMR of **342**

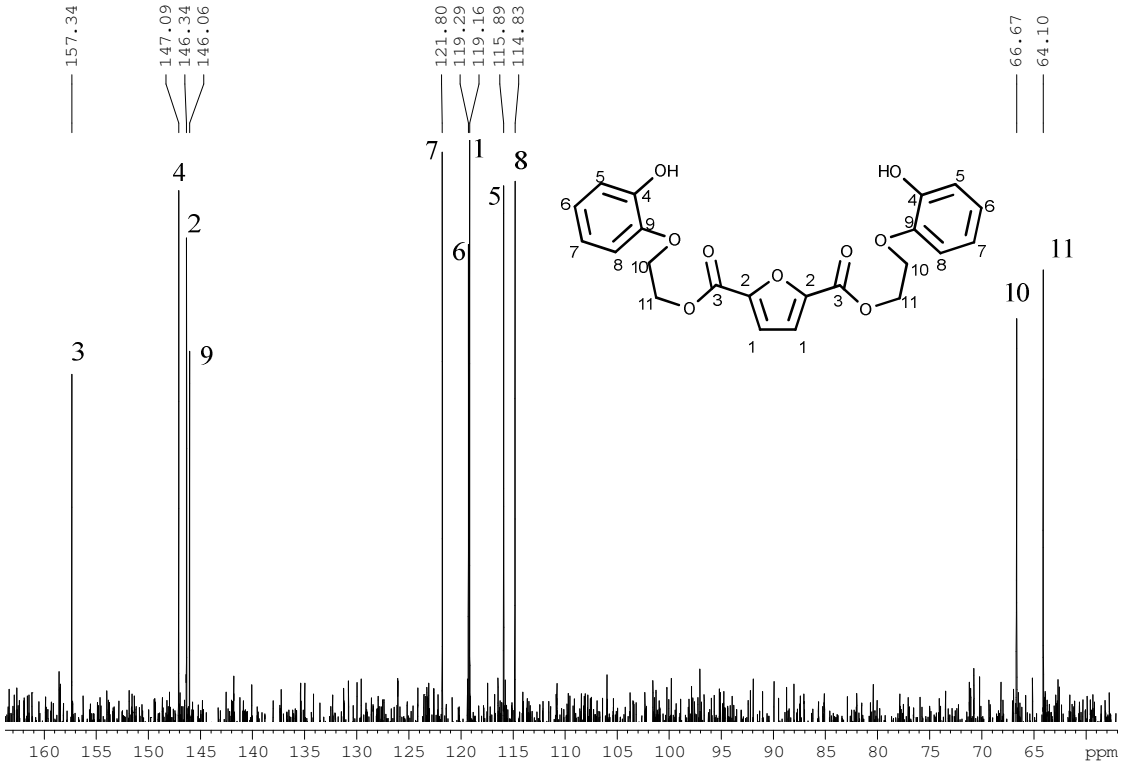


Figure 73: ^{13}C NMR of **356**

Atom Number	**342** ^{1}H Actual (Predicted)	**356** ^{1}H Actual (Predicted)	**342** ^{13}C Actual (Predicted)	**362** ^{13}C Actual (Predicted)	**366** Predicted ^{1}H (^{13}C)
1	7.43(7.81)	7.41(7.78)	121.55(120.6)	119.16(119.4)	7.72(119.4)
2			146.54(150.6)	146.34(146.9)	(148.4)
3			155.94(177.6)	157.34(158.9)	(158.9)
4			139.44(138.5)	147.09(148.8)	4.62(61.5)
5	7.21-7.13 (7.18)	6.79(6.84)	120.23(120.6)	115.89(116.5)	4.60(66.1)
6	6.98-6.94 (6.98)	6.79(6.84)	122.73(120.7)	119.29(121.7)	(145.6)
7	7.21-7.13 (7.15)	6.96(6.90)	127.51(126.1)	121.80(121.9)	6.82(115.8)
8	6.98-6.94 (6.96)	6.71-6.74 (6.82)	114.21(114.8)	114.82(115.8)	6.90(121.9)
9			149.79(153.9)	146.06(145.6)	6.84(121.7)
10	4.12(4.33)	4.29(4.60)	70.53(69.5)	66.67(66.1)	6.84(116.5)
11	3.79(3.69)	4.61(4.62)	61.04(60.9)	64.10(61.5)	(148.8)
12					7.87(120.6)
13					(149.1)
14					(177.6)
15					(138.5)
16					7.18(120.6)
17					6.98(120.7)
18					7.15(126.1)
19					6.96(114.8)
20					(153.9)
21					4.33(69.5)
22					3.69(60.9)

Table 15: Actual versus predicted ^{1}H and ^{13}C NMR of **342**, **356** *and predicted NMR values of* **366**.

The NMR spectra of both **342** and **356** closely match the predicted ^{1}H and ^{13}C NMR values for the two CH_2 moieties, positions 10 and 11. Although exact match was not observed it is in the correct area and demonstrates both are significantly different. Although the recorded data more closely resembles the predicted data for

compound **342** rather than for compound **356** they have still been shown to be significantly different and also dissimilar from the predicted NMR of **366**. These CH_2 moieties are the key for differentiating the two structures by NMR, as they are the hydrogens that will change most significantly and are also less likely to be complicated multiplets as seen in the aromatic regions.

When the NMR data is taken into account, with the wet chemistry test and the fact that the same methodology was used in the synthesis of these compounds as was used in each of the other pairs of isomers it seems almost certain that compounds **339** and **355** have been successfully isolated and correctly identified.

2.10.4: Differentiation between Structural Isomers **340** *and* **347:**

The possibility exists that under the right conditions **340** and **347** (figure 74) can undergo an intermolecular transesterification reaction transforming one product into the other, as previously outlined with the isomers in section 2.10.1.

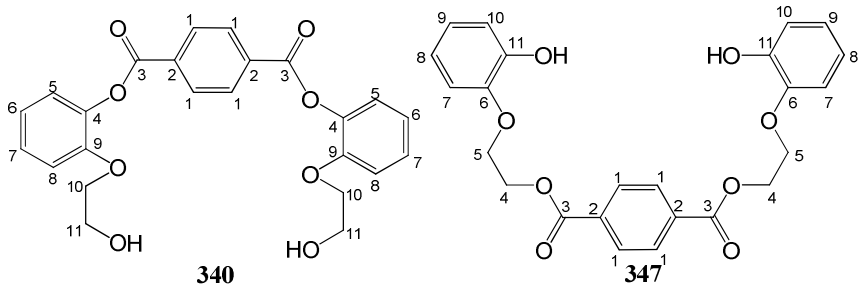
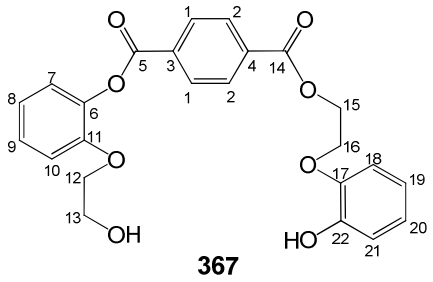


Figure 74: Side by side comparison of **340** *and* **347**.

The arguments for and against the possibility of the transesterification reaction occurring have been made in section 2.10.1, as such these arguments will be referred to when evaluating the evidence dividing to establish that **340** and **347** have been correctly synthesised and identified.

The intermolecular transesterification but this process would lead to **340** and **347** being interchangeable, but most notably would also lead to the creation of new product **367** as shown in figure 75 below.



367

Figure 75: Structure of **367**

The first test to be discussed here is a wet chemistry assay using iron(III) chloride to check for the presence for the phenol groups. In this case compound **340** gave negative results for the presence of the phenol with the iron(III) chloride solution remaining yellow and **347** gave positive results with the iron(III) chloride solution turning purple showing there was phenol present.

The ^{1}H and ^{13}C NMR spectra for **340** and **347** are shown in the figures 76 to 79 below. Below these figures in table 16 is a list of the actual versus predicted ^{1}H and ^{13}C NMR of **340** and **347** and the predicted peaks for **367**. Predictions were carried out using ChemBioDraw Ultra Version 11.0.1 © 1986-2007 CambridgeSoft.

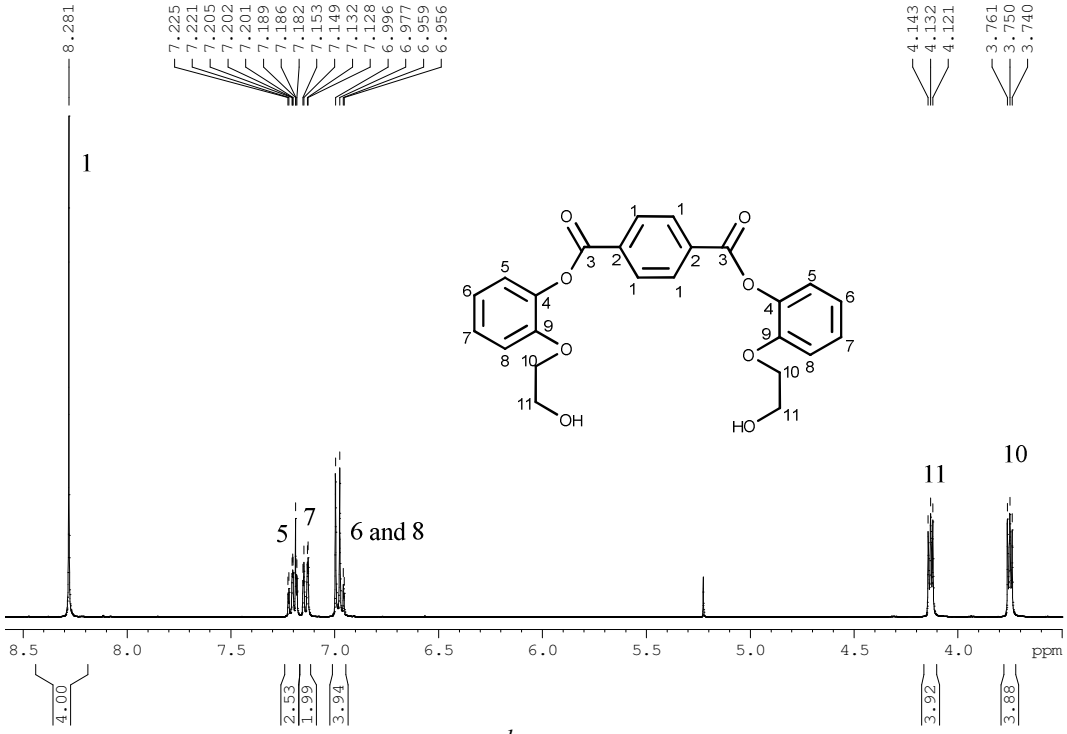


Figure 76: ^{1}H NMR of **340**.

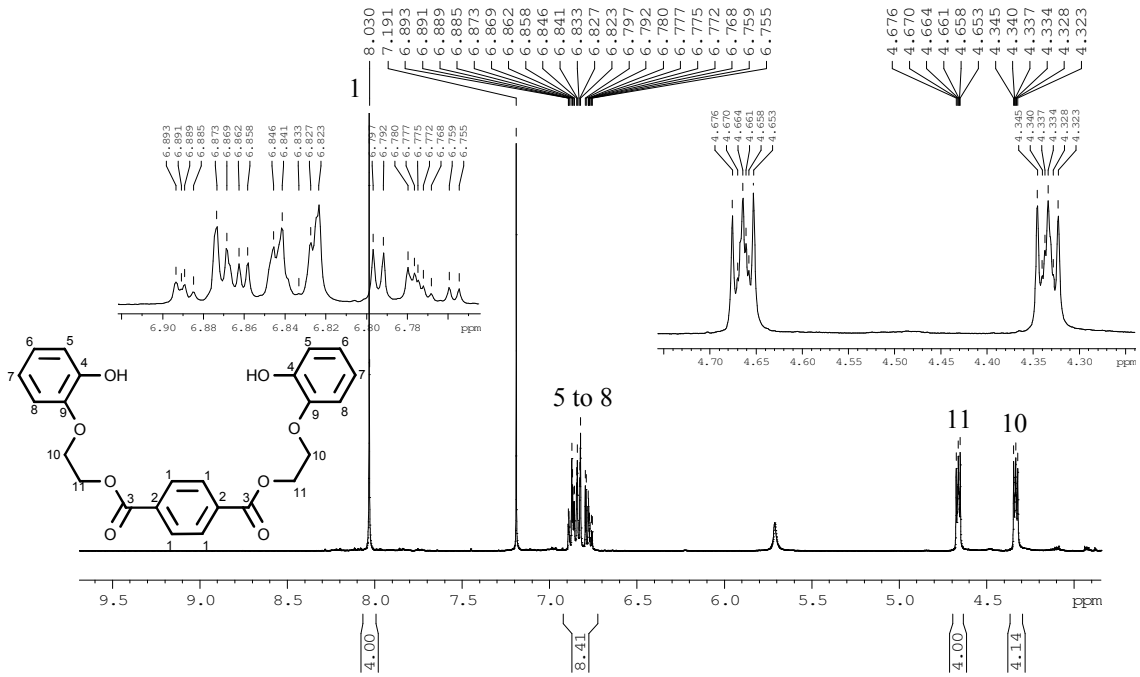


Figure 77: [1]H NMR of **347**.

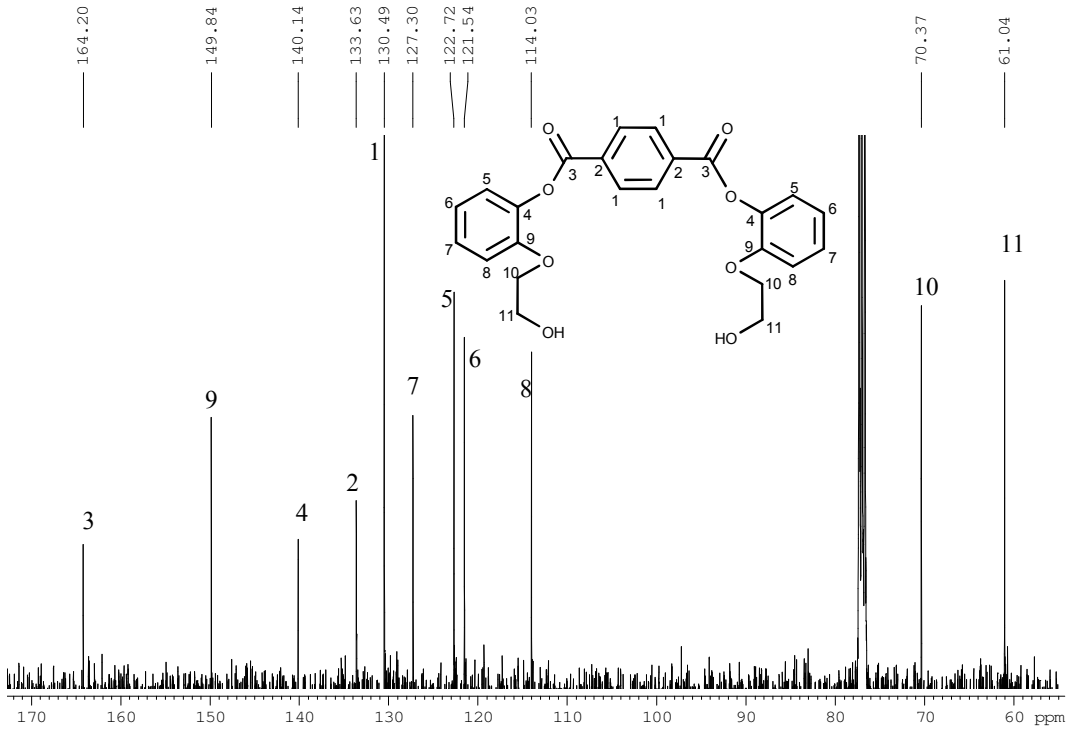


Figure 78: [13]C NMR of **340**.

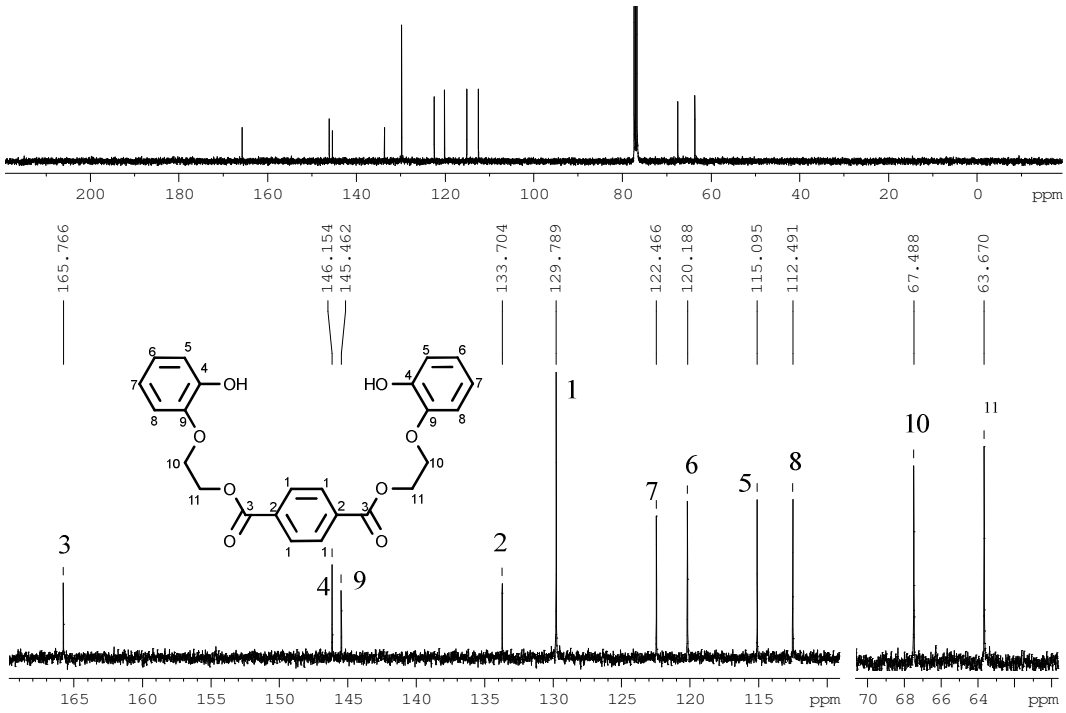


Figure 79: ^{13}C NMR of **347**.

Atom Number	**340** ^{1}H Actual (Predicted)	**347** ^{1}H Actual (Predicted)	**340** ^{13}C Actual (Predicted)	**347** ^{13}C Actual (Predicted)	**367** Predicted ^{1}H (^{13}C)
1	8.28(8.04)	8.08(7.83)	130.49(130.2)	129.79(129.8)	8.00(130.2)
2			133.64(135.4)	133.70(134.4)	7.87(129.8)
3			164.20(166.2)	166.77(166.9)	(134.5)
4			140.15(138.5)	146.15(148.8)	(135.3)
5	7.20(7.26)	6.89-6.75 (6.84)	122.73(120.6)	115.09(116.5)	(166.2)
6	6.99-6.95 (7.08)	6.89-6.75 (6.84)	121.55(120.7)	120.18(121.7)	(138.5)
7	7.14(7.24)	6.89-6.75 (6.90)	127.30(126.1)	122.47(121.9)	7.26(120.6)
8	6.99-6.95 (7.06)	6.89-6.75 (6.82)	114.05(114.8)	112.49(115.8)	7.08(120.7)
9			149.86(153.9)	145.46(145.6)	7.24(126.1)
10	3.75(4.33)	4.33(4.60)	70.37(69.5)	67.49(66.7)	7.06(114.8)
11	4.13(4.69)	4.66(4.62)	61.04(60.9)	63.67(63.9)	(153.9)
12					4.33(69.5)
13					3.69(60.9)
14					(166.9)
15					4.62(63.9)
16					4.60(66.7)
17					(145.6)
18					6.82(115.8)
19					6.90(121.9)
20					6.84(121.7)
21					6.84(116.5)
22					(148.8)

Table 16: Actual versus predicted ^{1}H and ^{13}C NMR of **340** *and* **347** *and the predicted peaks for* **367**.

In the case of **340** and **347** the predicted ^{1}H-NMR doest not match the actual data recorded for H10 and H11. Although the aromatic hydrogens of **347** closely match the

predicted values, it is hard to be certain how closely they match as they are in a very narrow region of the spectrum and all overlap. Also the aliphatic hydrogens, H10 and H11, in **347** appear closer together than in **340**, which matches the predicted pattern. This is not the ideal situation from the proton NMR as the aliphatic peaks are a more definitive indicator of the species as discussed above. H1 in the spectra of both **340** and **347** appear as a singlet above 8 ppm, again as with H10 and H11, they do not match the predicted chemical shift closely but instead appear in the predicted pattern with in their relative spectra. H1 in the spectrum of **340** appearing further downfield than H1in the spectrum of **347**. This is important as these hydrogens differ significantly between the two isomers.

The ^{13}C NMR spectra of these two compounds are also significantly different and each closely matches the predicted values for many of the carbons. Again these are not exact matches but are very close for almost all carbons in **340** and **347**. Also it must be noted that again none of the intermediate product **367** was isolated.

Also to be taken into account here are the macrocycles **352** and **358**, page 55. **352** has been synthesised, fully characterised and the X-ray crystal structure reported. Macrocycle **358** is the isomer of **352** and although no X-ray crystal data has been recorded, for **358**, it has been successfully isolated. Although this was not successfully synthesised directly from **340**, **358** was synthesised *via* the one pot method in which **340** had to form in the reaction vessel and then react with isophthaloyl dichloride to form the macrocycle (**358**). This is known to have happened because if 2-(2-hydroxyethoxy)phenol did not react with terephthaloyl dichloride first and then with isophthaloyl dichloride but instead reacted with isophthaloyl dichloride first, it would then have made **339** as the intermediate and formed macrocycle **352** as the product, as **339** has already been reported to be stable to the conditions for the synthesis of the macrocyclisation reaction. From this evidence it is known that **340** is formed preferentially to **347.**

When the NMR data is considered, with the wet chemistry test, the X-ray of macrocycle **352** and the fact that the same synthetic methodology was used for the synthesis each of the other isomeric pairs, it has been proven that compounds **340** and **347** have been unambiguously prepared.

2.11: Conclusion:

Thirteen novel crown ethers and eleven new precursors (both *bis*-alcohols and *bis*-phenols) were successfully synthesised and isolated. Six of these macrocycles were synthesised by at least 2 methods.

Sections 2.2 and 2.4 detail the isolation of the eleven precursors, seven *bis*-alcohols and four *bis*-phenols. Section 2.2 details the synthesis of the *bis*-alcohols **338**-**344** and Section 2.4 outlines the preparation of the *bis*-phenols **346**, **347**, **355** and **356**.

Sections 2.3, 2.5 and 2.6 discuss the formation of thirteen macrocycles. In section 2.3 the synthesis of seven macrocycles (**348**-**354**) made from the *bis*-alcohols was outlined. Section 2.5 addressed the synthesis of four macrocycles (**350**, **352**, **353** and **357**) from the *bis*-phenols. Section 2.6 discuses the one pot method used for the preparation of ten macrocycles (**351**-**354** and **357**-**362**) from 2-(2-hydroxyethoxy)phenol.

348 and **349** were isolated solely in section 2.3. **358**-**362** were only successfully prepared by the one pot synthesis, section 2.6. Each of the other macrocycles were synthesised by more then one method.

350 was successfully isolated by the methods in sections 2.3 and 2.5, with the latter giving the better yield (6 %). **351** and **354** were isolated in sections 2.3 and 2.6. **351** was isolated in higher yield (23 %) in section 2.6, the one pot method, while **354** was isolated in higher yield (12 %) in section 2.3 closing the *bis*-alcohol with the diacid dichloride. **352** and **353** were successfully isolated by all three methods. **352** was isolated in it's highest yield from the one pot method, 16 % compared to 3.5 % for each of the other methods, but **353** was isolated in it's highest yield (7 %), pre-optimisation, from the method utilising the *bis*-phenol to make the macrocycle, section 2.5. **357** was isolated in sections 2.5 and 2.6, with significantly higher yield (25 %) being isolated in section 2.5.

The one pot synthesis of **353** was optimised with the goal of using this optimised method to synthesise the analogous morphine containing macrocycle. This optimisation increased the yield from 2.5 % to 44 %. The use of this method for the synthesis of the morphine containing macrocycle will be discussed in chapter 3.

The results from the general synthesis and the optimisation of **353** suggest that the controlling factors for the isolatable yields of the macrocycles are related to temperature, time, concentration and equivalents of base used and not the general method used, as there was no clear general method which gave higher yields than each of the other methods.

The synthesis of *bis*(2-(2-hydroxyphenoxy)ethyl) 2,2-dimethylmalonate, **346**, was also optimised. This was done after biological testing indicated that **346** acted as a P-gp inhibitor. The yield for this compound was increased from 7 % to 62 %. The results of the biological testing will be discussed in chapter 5.

From the X-ray crystallographic data representative measurements of the cavity sizes in **352**, **353** and **363** have been presented. These measurements are based purely on physical size of the cavity in the solid state and do not take into account the rigidity/flexibility of the "hosts", the charge on any potential guests and the stability of the host-guest complex and therefore cannot be used as a predictable guide as to what guest species may bind to the macrocycles.

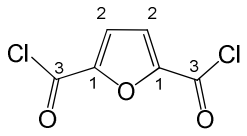
Using a combination of data from wet chemistry testing, NMR spectra, X-ray crystallography it has been clearly demonstrated that the isomers have been unequivocally identified.

In conclusion it has been demonstrated that a library of *bis*-alcohols, *bis*-phenols and macrocycles have been prepared. The macrocyclisation can be optimised to satisfactory yields and gram quantities of the model compounds can be obtained for screening.

Experimental:

All chemicals were purchased from Sigma/Aldrich and used as received. When necessary, solvents were purified prior to use and stored under nitrogen. Dichloromethane was distilled over CaH_2 and triethylamine was distilled and stored over potassium hydroxide pellets. Commercial grade reagents were used without further purification. Davisil 60A silica gel was used for thin layer and column flash chromatography. Melting points were determined using a Stuart melting point, SMP3, apparatus and are uncorrected. Infrared spectra were recorded on Perkin Elmer FT-IR spectrum GX spectrometer. Liquid chromatography time-of-flight mass spectrometry was recorded on a Waters Corp. Liquid Chromatography-Time of flight mass spectrometer from Micromass MS Technologies Centre. NMR spectra were obtained on a Bruker AC 400 NMR spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. The ^{1}H and ^{13}C NMR chemical shifts (ppm) are relative to tetramethylsilane. All coupling constants (*J*) are in Hertz.

Furan-2,5-dicarbonyl dichloride, 337:[66]



Mucic acid (10.0 g, 57.6 mmol) and *p*-toluenesulfonic acid monohydrate (31.7 g, 166.6 mmol) were stirred together at 140 ^{o}C for 2 hours. The reaction mixture was then cooled to 98 ^{o}C and aqueous 4 % calcium chloride solution (600 mL) was added and then heated to reflux with stirring for 1 hour. The resulting solution was then filtered and concentrated hydrochloric acid (200 mL) was added and left for twenty four hours at room temperature. This gave the furan-2,5-diacid as a pale red solid isolated by filtration.

This solid was then dried under vacuum and heated to reflux in excess thionyl chloride (26 mL) for sixteen hours. The excess thionyl chloride, sulfurochloridous acid and sulfurous acid (by-products of the reaction) were removed under vacuum to give the target product (12 %, 1.385 g, 7.177 mmol) as a pale red solid. As this product was an intermediate the exact mass was not recorded. The ^{1}H NMR and ^{13}C NMR are in agreement with the literature.[66]

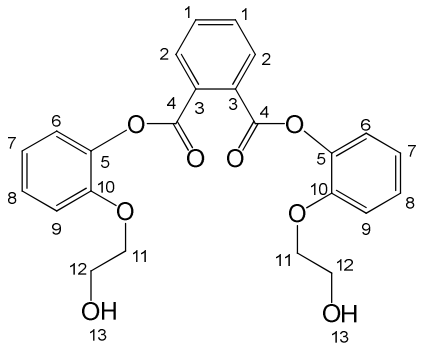
^{1}H NMR ($CDCl_3$): δ(ppm) 7.95 (2H, s, *H2*)

^{13}C NMR ($CDCl_3$): δ(ppm) 155.90 (*C3*), 149.34 (*C1*), 123.28 (*C2*)

IR (KBr disc): σ(cm^{-1}) 1812, 1549, 1507, 1384, 1201, 636

MP: 80-81 ^{o}C

***Bis*(2-(2-Hydroxyethoxy)phenyl) phthalate, 338:**



2-(2-Hydroxyethoxy)phenol (4.04 g, 20.0 mmol) was dissolved in dichloromethane (300 mL) at room temperature under a nitrogen atmosphere. To this was added triethylamine (10.0 mL, 72 mmol) and then chilled to -15 ^{o}C. The phthaloyl dichloride (1.44 mL, 10.0 mmol) was dissolved in dichloromethane (100 mL) and added slowly

to the mixture. After one hour at -15 ^{o}C the reaction was allowed to warm to room temperature and stirred for sixteen hours. The reaction was then quenched by the addition of DI water (DI H_2O) (10.0 mL), stirred for 20 minutes and then separated. The organic layer was washed with DI H_2O (30.0 mL X 3), dried over magnesium sulphate and the solvent was evaporated *in vacuo.* The product was purified by column chromatography on a silica stationary phase using 2:1 diethylether:dichloromethane, followed by recrystallisation from chloroform:hexane to obtain the pure product as a colourless solid (2.35 g, 54 %, 5.36 mmol).

^{1}H NMR ($CDCl_3$): δ(ppm) 7.63 (2H, dd, *J* = 3.4, 1.8 *Hz, H2*), 7.63 (2H, dd, *J* = 3.4, 1.8 *Hz, H1*), 716 (2H, td, *J* = 8.0, 1.6 *Hz, H6*), 7.09 (2H, dd, *J* = 8.0, 1.6 *Hz, H8*), 6.95 (2H, dd, *J* = 8.0, 1.2 *Hz, H9*), 6.90 (2H, td, *J* = 8.0, 1.2 *Hz, H7*), 4.04 (4H, t, *J* = 4.4 *Hz, H11*), 3.71 (4H, t, *J* = 4.4 *Hz, H12*), (2H, br s, H13).

^{13}C NMR ($CDCl_3$): δ(ppm) 166.46 (*C4*), 150.40 (*C10*), 139.66 (*C5*), 131.88 (*C1*), 131.57 (*C3*), 129.73 (*C2*), 127.37 (*C8*), 122.75 (*C7*), 121.11 (*C6*), 113.60 (*C9*), 70.36 (*C11*), 61.05 (*C12*)

IR (KBr disc): σ(cm^{-1}) 3430, 3068, 2943, 2878, 1722, 1607, 1572, 1458, 1410, 1267, 1180, 1109, 1076, 1056.

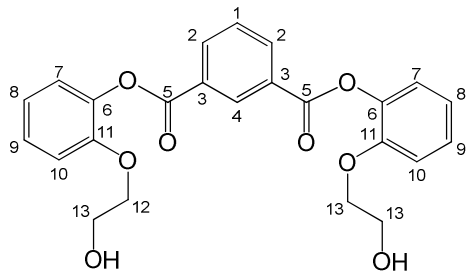
M.P.: 105-107 ^{o}C

Calculated exact mass for product: ($C_{24}H_{22}O_8$) 438.1315

Calculated exact mass for product + sodium: ($C_{24}H_{22}O_8Na^{+}$) 461.1207

Found: HRMS (EI, 70 eV) 461.1204

***Bis*(2-(2-Hydroxyethoxy)phenyl) isophthalate, 339:**



2-(2-Hydroxyethoxy)phenol (4.04 g, 20.0 mmol) was dissolved in dichloromethane (300 mL) at room temperature under a nitrogen atmosphere. Triethylamine (10.0 mL, 72 mmol) was added and the mixture was then cooled to -15 ^{o}C. Isophthaloyl dichloride (2.01 g, 10.0 mmol) was dissolved in dichloromethane (100 mL) and added slowly to the mixture. After one hour at -15 ^{o}C the reaction was allowed to warm to

room temperature and stirred for sixteen hours. The reaction was quenched by the addition of DI water (10.0 mL) stirred for 20 minutes and separated. The organic layer was washed with DI H_20 (30.0 mL X 3), dried over magnesium sulphate and the solvent was evaporated *in vacuo.* The product was purified by column chromatography on a silica stationary phase using 2:1 diethylether:dichloromethane followed by recrystallisation from chloroform:hexane to obtain the pure product as a colourless solid (93 %, 4.069 g, 9.30 mmol).

^{1}H NMR ($CDCl_3$): δ(ppm) 8.99 (1H, s, *H4*), 8.40 (2H, dd, *J* = 2.8 *Hz, H2*), 7.62 (1H, t, *J* = 2.8 *Hz, H1*), 7.21-7.12 (4H, m, *H's* 7 and 9), 6.98-6.94 (4H, m, *H's 8 and 10*), 4.12 (4H, t, *J* = 4.4 *Hz, H12*), 3.75 (4H, t, *J* = 4.4 *Hz, H13*)

^{13}C NMR (CDCl3): δ(ppm) 164.18 (*C5*), 149.90 (*C11*), 140.17 (*C6*), 135.21 (*C2*), 131.93 (*C3*), 130.03 (*C4*), 129.31 (*C1*), 127.22 (*C9*), 122.79 (*C8*), 121.50 (*C7*), 114.01(*C10*), 70.37 (*C12*), 61.01 (*C13*).

IR (KBr disc): σ(cm^{-1}) 3518, 3407, 3045, 2960, 2363, 1736, 1702, 1611, 1597, 1504, 1459, 1314, 1263, 1246, 1142, 1110, 1034.

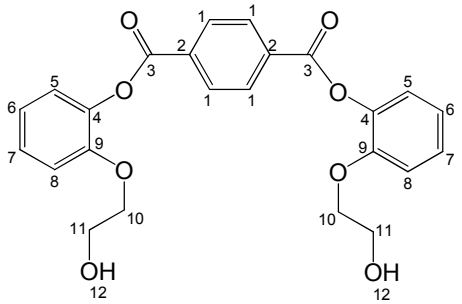
MP: 124-126 ^oC

Calculated exact mass for product: ($C_{24}H_{22}O_8$) 438.1315

Calculated exact mass for product + proton: ($C_{24}H_{22}O_8H^+$) 439.1387

Found: HRMS (EI, 70 eV) 439.1396

***Bis*(2-(2-Hydroxyethoxy)phenyl)terephthalate, 340:**



2-(2-Hydroxyethoxy)phenol (4.04 g, 20.0 mmol) was dissolved in dichloromethane (300 mL) at room temperature under a nitrogen atmosphere. To this was added triethylamine (10.0 mL, 72 mmol) and the mixture was cooled to -15 ^oC. Terephthaloyl dichloride (2.01 g, 10.0 mmol) was dissolved in dichloromethane (100 mL) and added slowly to the mixture. After one hour at -15 ^oC the reaction was allowed to warm to room temperature and stirred for sixteen hours. The reaction was quenched by the addition of DI water (10.0 mL) stirred for 20 minutes and then separated. The organic

layer washed with DI H_20 (30.0 mL X 3), dried over magnesium sulphate and the solvent was evaporated *in vacuo.* The product was purified by column chromatography on a silica stationary phase using 1:1 diethyl ether:dichloromethane giving the product as a colourless solid (67 %, 2.94 g, 6.70 mmol).

^{1}H NMR ($CDCl_3$): δ(ppm) 8.28 (4H, s, *H1*), 7.20 (2H, dt, *J* = 8.0, 1.6 *Hz H 7*), 7.14 (2H, dd, *J* = 8.4, 1.6 *Hz H 5*), 6.99-6.95 (4H, m, *H's 6 and 8*), 4.13 (4H, t, *J* = 4.4 *Hz, H11*), 3.75 (4H, t, *J* = 4.4 *Hz, H10*).

^{13}C NMR ($CDCl_3$): δ(ppm) 164.20 (*C3*), 149.86 (*C9*), 140.15 (*C4*), 133.64 (*C2*), 130.49 (*C1*), 127.30 (*C7*), 122.73 (*C5*), 121.55 (*C6*), 114.05 (*C8*), 70.37 (*C10*), 61.04 (*C11*).

IR (KBr disc): σ(cm^{-1})3449, 2963, 2365, 1736, 1607, 1458, 1407, 1261, 1179, 1102, 1068, 1015.

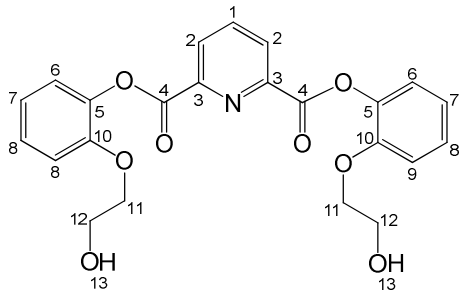
MP: 199-201 ^oC

Calculated exact mass for product: ($C_{24}H_{22}O_8$) 438.1315

Calculated exact mass for product + proton: ($C_{24}H_{22}O_8H^+$) 439.1387

Found: HRMS (EI, 70 eV) 439.1396

***Bis*(2-(2-Hydroxyethoxy)phenyl)pyridine-2,6-dicarboxylate, 341:**



2-(2-Hydroxyethoxy)phenol (308 mg, 2.00 mmol) was dissolved in dichloromethane (20.0 mL) at room temperature under a nitrogen atmosphere. Triethylamine was added (1.0 mL, 7.2 mmol) and the mixture was cooled to -15 ^oC. 2,6-Pyridine dicarbonyl dichloride (204 mg, 1.00 mmol) was dissolved in dichloromethane (20.0 mL) and added slowly to the mixture. After one hour at -15 ^oC the reaction was allowed to warm to room temperature and stirred for sixteen hours. The reaction was quenched by the addition of DI water (10.0 mL) stirred for 20 minutes and then separated. The organic layer washed with DI H_20 (30.0 mL X 3), dried over magnesium sulphate and the solvent was evaporated *in vacuo.* The product was purified by column

chromatography on a silica stationary phase using 1:1 ethylacetate:dichloromethane giving the product as a colourless solid (29 %, 0.128g, 0.29 mmol).

NMR ($CDCl_3$): δ(ppm) 8.25 (2H, d, *J* = 8.0 *Hz, H2*), 7.96 (1H, t, *J* = 1.6 *Hz, H1*), 6.87-6.72 (8H, m, *H's 6, 7, 8 and 9*), 4.74 (4H, t, *J* = 4.8 *Hz, H11*), 4.35 (4H, t, *J* = 4.8 *Hz, H12*).

^{13}C NMR (CD_3CN): δ(ppm) 164.43 (*C4*), 147.82 (*C10*), 146.57 (*C3*), 145.49 (*C1*), 138.44 (*C5*), 128.52 (*C2*), 122.53 (*C8*), 120.02 (*C7*), 115.59 (*C6*), 113.13 (*C9*), 67.34 (*C11*), 64.12 (*C12*).

IR (KBr disc): σ(cm^{-1}) 3498, 2961, 2365, 1730, 1637, 1596, 1504, 1458, 1404, 1374, 1323, 1246, 1175, 1141, 1112, 1083, 1064, 1035.

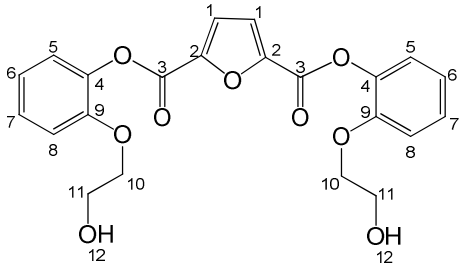
MP: 109-111 ^oC

Calculated exact mass for product: ($C_{23}H_{21}NO_8$) 439.1267

Calculated exact mass for product + proton: ($C_{23}H_{21}NO_8H^+$) 440.1340

Found: HRMS (EI, 70 eV) 440.1348

***Bis*(2-(2-Hydroxyethoxy)phenyl)furan-2,5-dicarboxylate, 342:**



2-(2-Hydroxyethoxy)phenol (4.04 g, 20.0 mmol) was dissolved in dichloromethane (300 mL) at room temperature under a nitrogen atmosphere. Triethylamine (10.0 mL, 72 mmol) was added and the mixture was cooled to -15 ^oC. 2,5-Furan dicarbonyl dichloride (2.029 g, 10.0 mmol) was dissolved in dichloromethane (100 mL) and added slowly to the mixture. After one hour at -15 ^oC the reaction was allowed to warm to room temperature and stirred for sixteen hours. The reaction was quenched by the addition of DI water (10.0 mL) stirred for 20 minutes and then separated. The organic layer was washed with DI H_20 (30.0 mL X 3), dried over magnesium sulphate and the solvent was evaporated *in vacuo.* The product was purified by column chromatography on a silica stationary phase using 1:1 ethylacetate:dichloromethane, followed by recrystallisation from chloroform:hexane to obtain the pure product as a colourless solid (1.46 g, 34 %, 3.41 mmol).

^{1}H NMR ($CDCl_3$): δ(ppm) 7.43 (2H, s, *H1*), 7.21-7.13 (4H, m, *H's 5 and 7*), 6.98-6.94 (4H, m, *H's 6 and 8*), 4.12 (4H, t, *J* = 4.4 *Hz, H10*), 3.79 (4H, t, *J* = 4.4 *Hz, H11*)

^{13}C NMR ($CDCl_3$): δ(ppm) 155.94 (*C3*), 149.79 (*C9*), 146.54 (*C2*), 139.44 (*C4*), 127.51 (*C7*), 122.73 (*C6*), 121.55 (*C1*), 120.23 (*C5*), 114.21 (*C8*), 70.53 (*C10*), 61.04 (*C11*).

IR (KBr disc): σ(cm^{-1}) 3371, 3127, 1713, 1688, 1583, 1505, 1468, 1438, 1357, 1326, 1305, 1281, 1265, 1223, 1168, 1132, 1112, 1063, 1047, 1023, 1006.

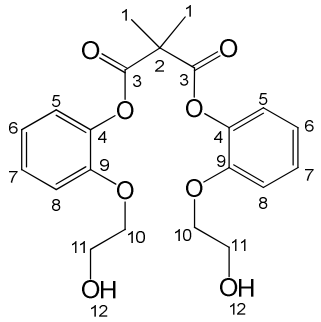
MP: 143-144 ^{o}C

Calculated exact mass for product: ($C_{22}H_{20}O_9$) 428.1107

Calculated exact mass for product + sodium: ($C_{22}H_{20}O_9Na^{+}$) 451.1000

Found: HRMS (EI, 70 eV) 451.1005

***Bis*(2-(2-Hydroxyethoxy)phenyl)-2,2-dimethylmalonate, 343:**



2-(2-Hydroxyethoxy)phenol (1.823 g, 11.84 mmol) was dissolved in dichloromethane (140 mL) at room temperature under a nitrogen atmosphere. Triethylamine (4.5 mL, 32 mmol) was added and the mixture was cooled to -15 ^{o}C. Dimethylmalonyl chloride (1.00 g, 5.92 mmol) was dissolved in dichloromethane (30 mL) and added slowly to the mixture. After one hour at -15 ^{o}C the reaction was allowed to warm to room temperature and stirred for sixteen hours. The reaction was quenched by the addition of DI water (10.0 mL) stirred for 20 minutes and then separated. The organic layer was washed with DI H_20 (30.0 mL X 3), dried over magnesium sulphate and the solvent was evaporated *in vacuo*. The product was purified by column chromatography on a silica stationary phase using 1:1 ethylacetate:chloroform to isolate the product (60 %, 1.10 g, 2.72 mmol) as a colourless solid.

^{1}H NMR ($CDCl_3$): δ(ppm) 7.15 (2H, td, *J* = 8.4, 1.6 *Hz, H5*), 7.02 (2H, dd, *J* = 8.8, 1.6 *Hz, H7*), 6.92-6.88 (4H, m, *H's 6 and 8*), 4.04 (4H, t, *J* = 4.4 *Hz, H10*), 3.71 (4H, t, *J* = 4.4 *Hz, H11*), 1.71 (6H, s, *H1*).

^{13}C NMR ($CDCl_3$): δ(ppm) 170.91 (*C3*), 150.11 (*C9*) 139.63 (*C4*), 127.33 (*C7*), 122.44 (*C6*), 121.18 (*C5*), 113.60 (*C8*) 70.29 (*C10*), 61.03 (*C11*), 50.45 (*C2*), 23.19 (*C1*).

IR (KBr disc): σ(cm^{-1}) 3531, 3451, 2996, 2954, 2924, 2878, 2363, 1754, 1607, 1504, 1459, 1391, 1309, 1292, 1254, 1213, 1181, 1144, 1099, 1067, 1032.

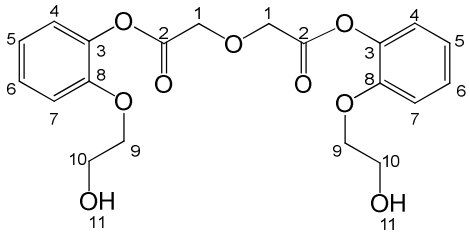
MP: 102-104 ^{o}C

Calculated exact mass for product: ($C_{21}H_{22}O_8$) 404.1471

Calculated exact mass for product + proton: ($C_{21}H_{22}O_8H^+$) 405.1544

Found: HRMS (EI, 70 eV) 405.1549

***Bis*(2-(2-Hydroxyethoxy)phenyl)diglycolate, 344:**



2-(2-Hydroxyethoxy)phenol (4.04 g, 20.0 mmol) was dissolved in dichloromethane (300 mL) at room temperature under a nitrogen atmosphere. Triethylamine (10.0 mL, 72 mmol) was added and the mixture was cooled to -15 ^{o}C. Diglycolyl dichloride (1.71 g, 10.0 mmol) was dissolved in dichloromethane (100 mL) and added slowly to the mixture. After one hour at -15 ^{o}C the reaction was allowed to warm to room temperature and stirred for sixteen hours. The reaction was quenched by the addition of DI water (10.0 mL) stirred for 20 minutes and then separated. The organic layer was washed with DI H_20 (30.0 mL X 3), dried over magnesium sulphate and the solvent was evaporated *in vacuo.* The product was purified by column chromatography on a silica stationary phase using 2:1 ether:dichloromethane, followed by recrystallisation from chloroform:hexane to isolate the pure product (76 %, 3.10 g, 7.63 mmol) as a colourless solid.

^{1}H NMR ($CDCl_3$): δ(ppm) 6.88-6.73 (8H, m, *H's 4 to 7*), 4.47 (4H, t, *J* = 4.2 *Hz, H9*), 4.21 (4H, s, *H1*), 4.19 (4H, t, *J* = 4.2 *Hz, H10*).

^{13}C NMR ($CDCl_3$): δ(ppm) 169.75 (C*2*), 146.12 (C*8*), 145.34 (C*3*), 122.50 (C*6*), 120.19 (C*5*), 115.19 (C*4*), 112.56 (C*7*), 68.25 (C*9*), 67.24 (C*1*), 63.14 (C*10*).

IR (KBr disc): σ(cm^{-1}) 3502, 3074, 2969, 2363, 1757, 1746, 1655, 1596, 1504, 1460, 1388, 1276, 1247, 1233, 1195, 1136, 1065, 1052, 1030.

MP: 67-69 ^{o}C

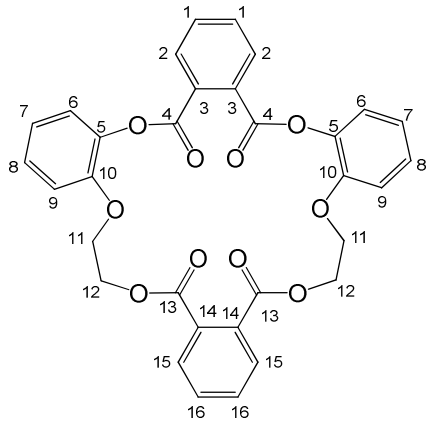
Calculated exact mass for product: ($C_{20}H_{22}O_9$) 406.1264

Calculated exact mass for product + proton: ($C_{20}H_{22}O_9H^+$) 407.1337

Found: HRMS (EI, 70 eV) 407.1342

Synthesis of the macrocycles from the bis-alcohols:

Synthesis of 2,3,6,7,10,11,17,18-tetrabenzo-1,4,9,12,15,20-hexaoxacyclodoeicosa-2,6,10,17-tetraene-5,8,16,19-tetraone, 348:



Bis(2-(2-Hydroxyethoxy)phenyl)phthalate, **338**, (0.438 g, 1.00 mmol) was dissolved in dry dichloromethane (25.0 mL) at room temperature and chilled to -15 ^oC. Dry triethylamine (0.7 mL, 5.0 mmol) was added. Phthaloyl dichloride (0.1426 mL, 1 mmol) was dissolved in dry dichloromethane (5.0 mL) and added slowly to the reaction mixture. The reaction mixture was stirred for 1 hour at -15 ^oC. After this period the reaction mixture was allowed to warm to room temperature and was stirred at sixteen hours. After this time had elapsed the reaction was quenched by adding distilled water (20.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X3), and followed by saturated ammonium chloride solution (50.0 mL) and with saturated sodium chloride solution (50.0 mL). The organic layer was dried over magnesium sulphate and the solvent *in vacuo*. The product was purified by column chromatography on a silica stationary phase with 2:1 diethylether:dichloromethane followed by recrystallisation from chloroform:hexane to give the final pure product (3.2 %, 18 mg, 0.032 mmol) as a colourless solid.

^1H NMR ($CDCl_3$): δ(ppm) 7.78 (2H, dd, *J* = 5.7, 3.3 *Hz, H2*), 7.49 (2H, dd, *J* = 5.7, 3.3 *Hz, H15*), 7.35-7.31 (4H, m, *H's 1 and 16*), 7.19-7.12 (4H, m, *H's 6 and 8*), 6.96 (2H,

dd, *J* = 8.2, 1.2 *Hz, H7*), 6.92 (2H, td, *J* = 7.7, 1.4 *Hz, H9*), 4.28 (4H, t, *J* = 4.2 *Hz, H12*), 4.15 (4H, t, *J* = 4.2 *Hz, H11*)

^{13}C NMR ($CDCl_3$): δ(ppm) 167.22 (*C13*), 165.21 (*C4*), 150.38 (*C10*), 140.42 (*C5*), 131.70 (*C1*), 131.41 (*C16*), 131.30 (*C3*), 130.89 (*C14*), 129.80 (*C2*), 128.76 (*C15*), 127.08 (*C8*), 123.04 (*C7*), 121.62 (*C6*), 114.35 (*C9*), 66.69 (*C11*), 63.61 (*C12*).

IR (KBr disc): σ(cm^{-1}) 3445, 3040, 2929, 2878, 1734, 1606, 1581, 1505, 1452, 1434, 1414, 1403, 1372, 1256, 1191, 1162, 1111, 1050.

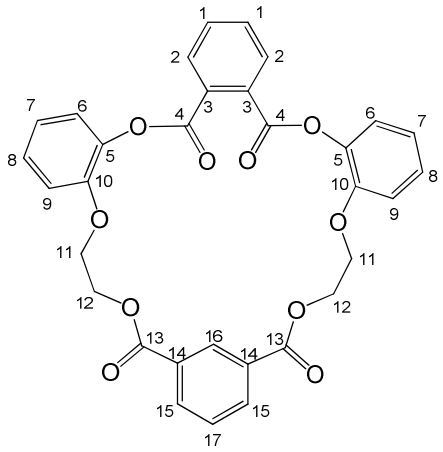
MP: 122-124 ^oC

Calculated exact mass for product: ($C_{32}H_{24}O_{10}$) 568.1369

Calculated exact mass for product + proton: ($C_{32}H_{24}O_{10}H^+$) 569.1442

Found: HRMS (EI, 70 eV) 569.1464

Synthesis of 2,3,6,7,10,11,17,19-tetrabenzo-1,4,9,12,15,21-hexaoxacyclotrieicosa-2,6,10,17-tetraene-5,8,16,20-tetraone, 349:



Bis(2-(2-Hydroxyethoxy)phenyl)phthalate, **338**, (0.438 g, 1.00 mmol) was dissolved in dry dichloromethane (25.0 mL) at room temperature and chilled to -15 ^oC. Dry triethylamine (0.7 mL, 5.0 mmol) was added. Isophthaloyl dichloride (0.201 g, 1.00 mmol) was dissolved in dry dichloromethane (5.0 mL) and added slowly to the reaction mixture. The reaction mixture was stirred for 1 hour at -15 ^oC. The reaction mixture was allowed to warm to room temperature and was stirred for sixteen hours. After this time the reaction was quenched by adding distilled water (20.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X3), and saturated ammonium chloride solution (50.0 mL) and with saturated sodium chloride solution (50.0 mL). The organic layer was dried

over magnesium sulphate and then the solvent was removed *in vacuo*. The product was purified by column chromatography on a silica stationary phase with 3:1 diethyl ether:chloroform followed by recrystallisation from chloroform:hexane to isolate the pure product (1.9 %, 11 mg, 0.019 mmol) as a colourless solid.

^{1}H NMR ($CDCl_3$): δ(ppm) 8.26 (1H, s, *H16*), 8.09 (2H, d, *J* = 7.6 *Hz, H15*), 7.68 (2H, dd, *J* = 3.4, 5.3 *Hz, H2*), 7.40 (1H, t, *J* = 7.7 *Hz, H17*), 7.28-7.22 (4H, m, *H's 1 and 6*), 7.17 (2H, d, *J* = 8.0 *Hz, H8*), 7.12 (2H, d, *J* = 8.0 *Hz, H7*), 7.02 (2H, t, *J* = 7.5 *Hz, H9*), 4.59 (4H, br d, *J* = 2.8 *Hz, H12*), 4.33 (4H, br s, *H11*)

^{13}C NMR ($CDCl_3$): δ(ppm) 165.78 (*C13*), 164.82 (*C4*), 150.05 (*C10*), 141.39 (*C5*), 134.04 (*C15*), 131.15 (*C1*), 131.00 (*C3*), 130.12 (*C14*), 130.02 (*C16*), 129.25 (*C2*), 127.96 (*C17*), 127.00 (*C6*), 122.95 (*C9*), 122.48 (*C8*), 115.96 (*C7*), 67.80 (*C11*), 63.71 (*C12*).

IR (KBr disc): σ(cm^{-1}) 3079, 2942, 1780, 1723, 1606, 1501, 1453, 1407, 1378, 1254, 1190, 1143, 1105, 1084, 1044.

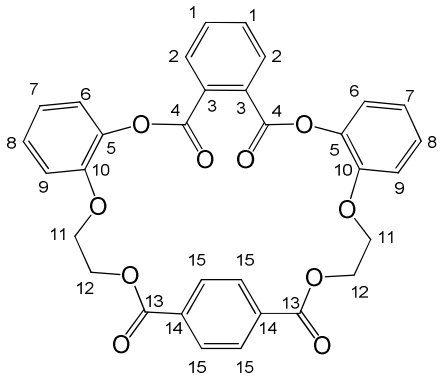
MP: 223.5-225 ^{o}C

Calculated exact mass for product: ($C_{32}H_{24}O_{10}$) 568.1369

Calculated exact mass for product + proton: ($C_{32}H_{24}O_{10}H^{+}$) 569.1442

Found: HRMS (EI, 70 eV) 569.1464

Synthesis of 2,3,6,7,10,11,17,20-tetrabenzo-1,4,9,12,15,22-hexaoxacyclotetraeicosa-2,6,10,17,19-pentaene-5,8,16,21-tetraone, 350:



Bis(2-(2-hydroxyethoxy)phenyl)phthalate, **338**, (0.438 g, 1.00 mmol) was dissolved in dry dichloromethane (25.0 mL) at room temperature and chilled to -15 ^{o}C. Dry triethylamine (0.7 mL, 5.0 mmol) was added. Terephthaloyl dichloride (0.201 g, 1.00 mmol) was dissolved in dry dichloromethane (5.0 mL) and added slowly to the reaction mixture. The reaction mixture was stirred for 1 hour at -15 ^{o}C. After this

period the reaction mixture was allowed to warm to room temperature and was stirred for sixteen hours. The reaction was quenched by adding distilled water (20.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X3), and saturated ammonium chloride solution (50.0 mL) and with saturated sodium chloride solution (50.0 mL). The organic layer was dried over magnesium sulphate and the solvent was removed *in vacuo*. The product was purified by column chromatography on a silica stationary phase with 2:1 diethylether:dichloromethane followed by recrystallisation from chloroform:hexane to isolate the pure product (3.7 %, 21 mg, 0.037 mmol) as a colourless solid.

^{1}H NMR ($CDCl_3$): δ(ppm) 7.74 (2H, dd, *J* = 5.7, 3.3 *Hz, H2*), 6.67 (4H, s, *H15*), 7.35 (2H, dd, *J* = 8.0, 1.6 *Hz, H6*), 7.20-7.15 (4H, m, *H's 1 and 8*), 6.99-6.95 (4H, m, *H's 7 and 9*), 4.59 (4H, v.br. s, *H12*), 4.32 (4H, v.br. s, *H11*).

^{13}C NMR ($CDCl_3$): δ(ppm) 165.72 (*C13*), 164.63 (*C4*), 149.89 (*C10*), 140.24 (*C5*), 133.09 (*C14*), 131.44 (*C1*), 131.24 (*C3*), 129.41 (*C15*), 129.36 (*C2*), 126.79 (*C8*), 123.76 (*C6*), 121.70 (*C7*), 114.18 (*C9*), 66.60 (*C11*), 62.90 (*C12*).

IR (KBr disc): σ(cm^{-1}) 3446, 2952, 1721, 1605, 1501, 1456, 1410, 1370, 1276, 1256, 1180, 1106, 1045.

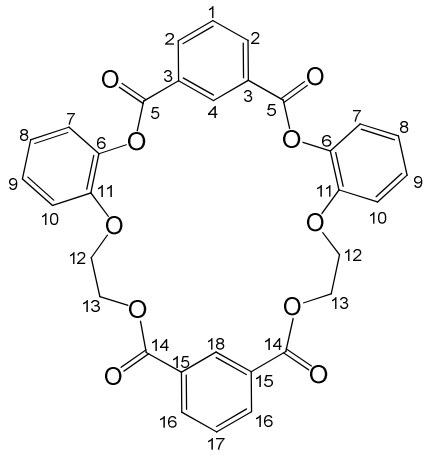
MP: 173-174^{o}C

Calculated exact mass for product: ($C_{32}H_{24}O_{10}$) 568.1369

Calculated exact mass for product + proton: ($C_{32}H_{24}O_{10}H^{+}$) 569.1442

Found: HRMS (EI, 70 eV) 569.1464

Synthesis of 2,3,6,8,11,12,18,20-tetrabenzo-1,4,10,13,16,22-hexaoxacyclotetraicosa-2,6,11,18-tetraene-5,9,17,21-tetraone, 351:



Bis(2-(2-Hydroxyethoxy)phenyl) isophthalate, **339**, (0.438 g, 1.00 mmol) was dissolved in dry dichloromethane (25.0 mL) at room temperature and chilled to -15 ^{o}C. Dry triethylamine (0.7 mL, 5.0 mmol) was added. Isophthaloyl dichloride (0.201 g, 1.00 mmol) was dissolved in dry dichloromethane (5.0 mL) and added slowly to the reaction mixture. The reaction mixture was stirred for 1 hour at -15 ^{o}C. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature for sixteen hours. After this time the reaction was quenched by adding distilled water (20.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X3), and saturated ammonium chloride solution (50.0 mL) and with saturated sodium chloride solution (50.0 mL). The organic layer was dried over magnesium sulphate and the solvent was removed *in vacuo*. The product was purified by column chromatography on a silica stationary phase with 1:1 diethyl ether:chloroform followed by recrystallisation from toluene yielding the pure product (4.4 %, 0.025 g, 0.044 mmol) as a colourless solid.

^{1}H NMR ($CDCl_3$): δ(ppm) 8.37 (1H, t, *J* = 1.6 *Hz, H4*), 8.15 (2H, dd, *J* = 7.6, 1.6 *Hz, H2*), 8.06 (1H, t, *J* = 1.6 *Hz, H18*), 8.02 (2H, dd, *J* = 7.6 , 1.6 *Hz, H16*), 7.35(2H, td, *J* = 7.2, 1.6 *Hz, H7*), 7.17-7.21 (2H, m, *H's 1 and 17*), 7.05 (2H, dd, *J* = 7.6, 1.6 *Hz, H9*), 6.97 (4H, td, *J* = 4.1, 1.2 *Hz, H's 8 and 10*), 4.62 (4H, t, *J* = 4.2 *Hz, H13*), 4.30 (4H, t, *J* = 4.2 *Hz, H12*).

^{13}C NMR (CDCl3): δ(ppm) 165.36 (*C14*), 163.66 (*C5*), 150.08 (*C11*), 140.28 (*C6*), 134.41 (*C2*), 133.82 (*C16*), 131.45 (*C15*), 130.66 (*C4*), 129.94 (*C3*), 129.66 (*C18*),

128.61 (*C1*), 128.34 (*C17*), 128.25 (*C9*), 127.11 (*C8*), 123.16 (*C6*), 121.67 (*C7*), 113.74 (*C10*), 66.83 (*C12*), 60.65 (*C13*).

IR (KBr disc): σ(cm^{-1}) 3087, 2968, 2364, 1728, 1607, 1506, 1459, 1431, 1405, 1375, 1308, 1293, 1263, 1231, 1187, 1163, 1114, 1058, 1001.

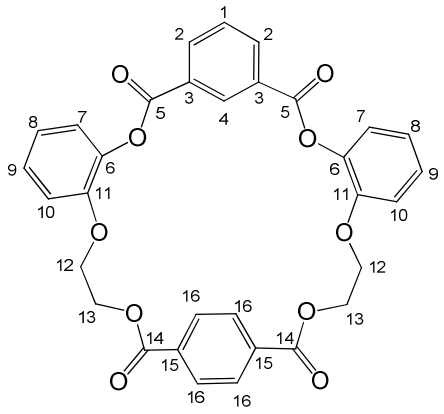
MP: 176-178 ^{o}C

Calculated exact mass for product: ($C_{32}H_{24}O_{10}$) 568.1369

Calculated exact mass for product + proton: ($C_{32}H_{24}O_{10}H^{+}$) 569.1442

Found: HRMS (EI, 70 eV) 569.1448

Synthesis of 2,3,6,8,11,12,18,21-tetrabenzo-1,4,10,13,16,23-hexaoxacyclopenta-icosa-2,6,11,18,20-pentaene-5,9,17,22-tetraone, 352:



Bis(2-(2-Hydroxyethoxy)phenyl) isophthalate, **339**, (0.438 g, 1.00 mmol) was dissolved in dry dichloromethane (25.0 mL) at room temperature and chilled to -15 ^{o}C. Dry triethylamine (0.7 mL, 5.0 mmol) was added. Terephthaloyl dichloride (0.201 g, 1.00 mmol) was dissolved in dry dichloromethane (5.0 mL) and added slowly to the reaction mixture. The reaction mixture was stirred for 1 hour at -15 ^{o}C. The reaction mixture was allowed to warm to room temperature and was stirred for sixteen hours. After this time had elapsed the reaction was quenched by adding distilled water (20.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X3), and saturated ammonium chloride solution (50.0 mL) and with saturated sodium chloride solution (50.0 mL). The organic layer was dried over magnesium sulphate and then the solvent was removed *in vacuo*. The product was purified by column chromatography on a silica stationary phase with 3:1 diethylether:chloroform followed by recrystallisation from chloroform:hexane yielding the pure product (3.5 %, 0.020 g, 0.035 mmol) as a colourless solid.

^{1}H NMR ($CDCl_3$): δ(ppm) 8.72 (1H, t, *J* = 1.6 *Hz, H4*), 8.27 (2H, dd, *J* = 8.0, 1.6 *Hz, H2*), 7.64 (4H, s, *H16*), 7.41 (1H, t, *J* = 8.0 *Hz, H1*), 7.22 (2H, td, *J* = 7.6, 1.6 *Hz, H9*), 7.06 (4H, td, *J* = 8.0, 1.2 *Hz, H's 7 and 8*), 6.99 (2H, td, *J* = 7.6, 1.2 *Hz, H10*), 4.57 (4H, t, *J* = 4.4 *Hz, H13*), 4.34 (4H, t, *J* = 4.4 *Hz, H12*).

^{13}C NMR ($CDCl_3$): δ(ppm) 165.49 (*C14*), 163.74 (*C5*), 149.89 (*C11*), 140.63 (*C6*), 134.49 (*C2*), 133.33 (*C15*), 131.88 (*C4*), 130.22 (*C3*), 129.24 (*C16*), 128.97 (*C1*), 127.30 (*C9*), 123.44 (*C7*), 122.14 (*C8*), 114.86 (*C10*), 66.80 (*C12*), 62.85 (*C13*).

IR (KBr disc): σ(cm^{-1}) 3077, 2947, 2925, 2875, 1951, 1750, 1722, 1605, 1504, 1451, 1413, 1381, 1253, 1221, 1184, 1126, 1081, 1046, 1018.

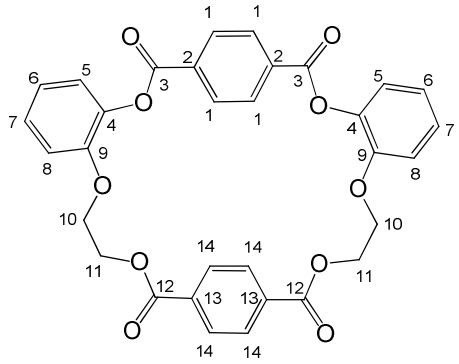
MP: 197-199 ^oC

Calculated exact mass for product: ($C_{32}H_{24}O_{10}$) 568.1369

Calculated exact mass for product + proton: ($C_{32}H_{24}O_{10}H^+$) 569.1442

Found: HRMS (EI, 70 eV) 569.1448

Synthesis of 2,3,6,9,11,12,13,19,22-tetrabenzo-1,4,11,14,17,24-hexaoxacyclohexa-icosa-2,6,8,12,19,21-hexaene-5,10,18,23-tetraone, 353:



Bis(2-(2-Hydroxyethoxy)phenyl) terephthalate, **340**, (0.438 g, 1.00 mmol) was dissolved in dry dichloromethane (25.0 mL) at room temperature and chilled to -15 ^oC. Dry triethylamine (0.7 mL, 5.0 mmol) was added. Terephthaloyl dichloride (0.201 g, 1.00 mmol) was dissolved in dry dichloromethane (5.0 mL) and added slowly to the reaction mixture. The reaction mixture was stirred for 1 hour at -15 ^oC. The reaction mixture was then allowed to warm to room temperature and was stirred for sixteen hours. After this time had elapsed the reaction was quenched by adding distilled water (20.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X3), and saturated ammonium chloride solution (50.0 mL) and saturated sodium chloride solution (50.0 mL). The organic

layer was then dried over magnesium sulphate and then the solvent was removed *in vacuo*. The product was purified by column chromatography on a silica stationary phase with 3:1 diethylether:chloroform followed by recrystallisation from toluene yielding the pure product (2.5 %, 0.014 g, 0.025 mmol) as a colourless solid.

^{1}H NMR ($CDCl_3$): δ(ppm) 8.13 (4H, s, *H1*), 7.74 (4H, s, *H14*), 7.31 (2H, td, *J* = 5.3, 1.2 *Hz, H5*), 7.19 (4H, qd, *J* = 8.*0,* 1.2 *Hz, H6*), 7.16 (2H, dd, *J* = 8.0*,* 1.2 *Hz, H7*), 7.09 (2H, td, *J* = 5.3, 1.2 *Hz, H8*), 4.65 (4H, t, *J* = 4.2 *Hz, H11*), 4.45 (4H, t, *J* = 4.2 *Hz, H10*).

^{13}C NMR ($CDCl_3$): δ(ppm) 165.81 (*C12)*, 164.20 (*C3)*, 150.17 (*C9)*, 141.20 (*C4)*, 133.92 (*C2)*, 133.74 (*C13)*, 130.48 (*C1)*, 129.69 (*C14)*, 127.69 (*C7)*, 123.75 (*C6)*, 122.68 (*C5)*, 115.83 (*C8)*, 67.59 (*C11)*, 63.53 (*C10).*

IR (KBr disc): σ(cm^{-1}) 2963, 2364, 1944, 1736, 1607, 1578, 1501, 1457, 1407, 1376, 1247, 1179, 1112, 1068, 1014.

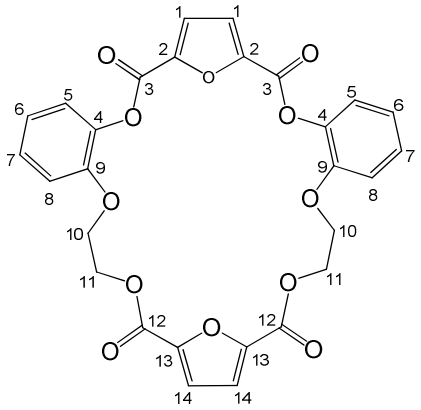
MP: 194-194 ^{o}C

Calculated exact mass for product: ($C_{32}H_{24}O_{10}$) 568.1369

Calculated exact mass for product + proton: ($C_{32}H_{24}O_{10}H^{+}$) 569.1442

Found: HRMS (EI, 70 eV) 569.1448

Synthesis of 2,3,11,12,-dibenzo-6,8,18,20-difurano-1,4,7,10,13,16,19,22-octaoxacyclohexaeicosa-2,11-diaene-5,9,17,21-tetraone, 354:



Bis(2-(2-Hydroxyethoxy)phenyl) furan-2,5-dicarboxylate, **342**, (0.101 g, 0.236 mmol) was dissolved in dry dichloromethane (20.0 mL) at room temperature and chilled to -15 ^{o}C. Dry triethylamine (0.25 mL, 1.8 mmol) was added. Furan-2,5-dicarbonyl dichloride (0.046 g, 0.236 mmol) was dissolved in dry dichloromethane (20.0 mL) and added slowly to the reaction mixture. The reaction mixture was stirred for 1 hour at -15 ^{o}C. The reaction mixture was allowed to warm to room temperature and was stirred at

room temperature for sixteen hours. After this time had elapsed the reaction was quenched by adding distilled water (20.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X3), and saturated ammonium chloride solution (50.0 mL) and saturated sodium chloride solution (50.0 mL). The organic layer was then dried over magnesium sulphate and then the solvent was removed *in vacuo*. The product was purified by column chromatography on a silica stationary phase with dichloromethane followed by recrystallisation from chloroform:hexane isolating the pure product (12 %, 0.016 g, 0.029 mmol) as a colourless solid.

^{1}H NMR (ACN-d_3): δ(ppm) 7.34-7.29 (4H, m, *H's 5 and 7*), 7.20-7.15 (6H, m, *H's 1, 6 and 14*), 7.05 (2H, td, *J* = 7.0, 1.4 *Hz, H8*), 4.56 (4H, t, *J* = 4.4 *Hz, H11*), 4.36 (4H, t, *J* = 4.4 *Hz, H10*)

^{13}C NMR ($CDCl_3$): δ(ppm) 169.68 (*C12*), 157.91 (*C3*), 155.03 (*C9*), 149.54 (*C2*), 146.14 (*C13*), 127.44 (*C4*), 124.43 (*C7*), 122.75 (*C5*), 121.42 (*C6*), 119.37 (*C1*), 118.38 (*C14*), 114.31 (*C8*), 66.30 (*C10*), 62.40 (*C11*).

IR (KBr disc): σ(cm^{-1}) 3137, 2928, 1742, 1720, 1610, 1586, 1505, 1460, 1407, 1379, 1289, 1226, 1188, 1158, 1126, 1024.

MP: Turned from a colourless solid to a brown solid at 204 ^{o}C, did not melt below 300 ^{o}C

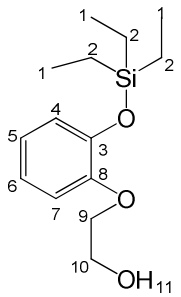
Calculated exact mass for product: ($C_{28}H_{20}O_{12}$) 548.0955

Calculated exact mass for product + sodium: ($C_{28}H_{20}O_{12}Na^{+}$) 571.0847

Found: HRMS (EI, 70 eV) 571.0852

Methods for *bis*-phenols linked between the primary alcohols:

2-(2-(Triethylsilyloxy)phenoxy)ethanol, 345:



2-(2-Hydroxyethoxy)phenol (1.54 g, 10.0 mmol) was dissolved dry dichloromethane (30.0 mL) under nitrogen at room temperature. Triethylamine (1.4 mL, 10 mmol) was added. TES triflate (2.26 mL, 2.643 g, 10.0 mmol) was added to the reaction mixture. This was stirred for 48 hours. The reaction mixture was transferred to a separation funnel and was washed with distilled water (30.0 mL X4), saturated NH_4Cl solution (40.0 mL X2). The organic layer was then dried over $MgSO_4$ and the solvent was removed *in vacuo*.

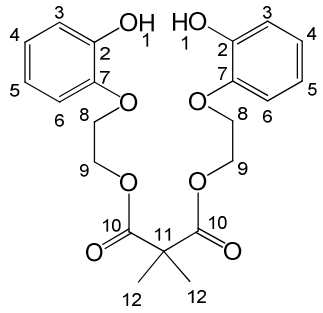
The product was purified by column chromatography on a silica stationary phase using dichloromethane isolating pure product (97 %, 1.301 g, 9.7 mmol) as a pale yellow liquid. As this product was an intermediate its infrared spectrum and exact mass were not recorded.

^{1}H NMR ($CDCl_3$): δ(ppm) 7.03-6.95 (2H, m, *H's 5 and 7*), 6.86-6.82 (2H, m, *H's 4 and 6*), 4.11 (2H, t, *J* = 4.7 *Hz, H9*), 3.85 (2H, t, *J* = 4.7 *Hz, H10*), 1.04 (9H, t, *J* = 8.0 *Hz, H1*), 0.72 (6H, q, *J* = 8.0 *Hz, H2*).

^{13}C NMR ($CDCl_3$): δ(ppm) 147.94 (*C9*), 146.21 (*C3*), 123.40 (*C6*), 119.87 (*C4*), 116.61 (*C5*), 115.68 (*C7*), 72.90 (*C9*), 61.70 (*C10*), 6.67 (*C2*), 4.26 (*C1*).

Synthesis of bis-phenols from triethylsilyl protected 2-(2-hydroxyethoxy)phenol:

***Bis*(2-(2-Hydroxyphenoxy)ethyl)-2,2-dimethylmalonate, 346:**



2-(2-(Triethylsilyloxy)phenoxy)ethanol, **345**, (2.220 g, 8.27 mmol) was dissolved in dry dichloromethane (93.0 mL) at room temperature. Dry triethylamine (3.73 mL, 27.8 mmol) was added whilst stirring. Dimethylmalonyl chloride (0.55 mL, 4.14 mmol) was then added slowly to the reaction mixture. The reaction mixture was stirred for 48 hours. The reaction was quenched by adding distilled water (20.0 mL) and stirring for ten minutes. The organic and aqueous layers were separated. The organic layer was washed with distilled water (20.0 mL X5), dried over magnesium sulphate and the solvent was removed *in vacuo* yielding the crude intermediate product. This was purified by column chromatography on a silica stationary phase using 3:1 diethyl ether:chloroform as the mobile phase to isolate the pure intermediate product.

The intermediate was dissolved in 4:1 acetic acid:water mixture (16.0 mL). This was stirred at 40 ^{o}C and monitored by TLC every 10 minutes with 3:1 diethyl ether:chloroform. When the reaction had gone to completion it was quenched by the addition of saturated sodium carbonate until the acid was neutralised and dichloromethane to keep the product in solution. The solution was transferred to a separating funnel. The organic layer was extracted and then washed with distilled water (50.0 mL X4), and saturated sodium bicarbonate solution (20.0 mL X4). The organic layer was dried over $MgSO_4$ and then the solvent was removed *in vacuo*.

The product was then recrystallised from chloroform:hexane to isolate the pure product (64 %, 1.074 g, 2.64 mmol) as a colourless solid.

^{1}H NMR ($CDCl_3$): δ(ppm) 7.08 (2H, dt, *J* = 7.8, 1.0 *Hz, H4*), 6.98 (2H, dd, *J* = 7.8*,* 1.0 *Hz, H6*), 6.86–6.82 (4H, m, *H's 3 and 5*), 3.94 (4H, t, *J* = 4.4 *Hz, H9*), 3.64 (4H, broad s, *H8*), 1.67 (6H, s, *H12*).

^{13}C NMR ($CDCl_3$): δ(ppm) 169.91 (*C10*), 149.06 (*C2*), 138.54 (*C7*), 126.28 (*C5*), 121.35 (*C4*), 120.07 (*C3*), 112.58 (*C6*), 69.14 (*C8*), 59.87 (*C9*), 49.36 (*C11*), 22.08 (*C12*).

IR (KBr disc): σ(cm^{-1}) 3531, 3452, 3123, 3066, 2996, 2954, 2878, 2564, 2363, 1938, 1753, 1607, 1504, 1459, 1412, 1391, 1371, 1255, 1144, 1100.

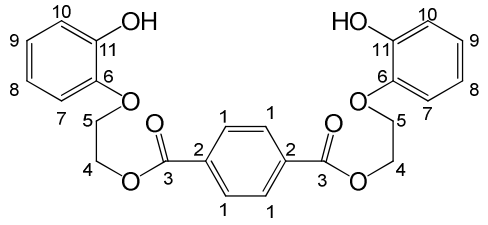
MP: 100-101 ^oC

Calculated exact mass for product: ($C_{21}H_{22}O_8$) 404.1471

Calculated exact mass for product + proton: ($C_{21}H_{22}O_8H^+$) 405.1544

Found: HRMS (EI, 70 eV) 405.1549

***Bis*(2-(2-Hydroxyphenoxy)ethyl)terephthalate, 347:**



2-(2-(Triethylsilyloxy)phenoxy)ethanol, **345**, (2.276 g, 8.4 mmol) was dissolved in dry dichloromethane (60.0 mL) at room temperature. Dry triethylamine (4.2 mL, 30 mmol) was added whilst stirring. Terephthaloyl dichloride (0.848 g, 4.2 mmol) was added slowly to the reaction mixture. The reaction mixture was stirred for 48 hours. The reaction was quenched by addition of distilled water (20.0 mL) and stirring for ten minutes. The organic and aqueous layers were separated. The organic layer was washed with distilled water (20.0 mL X5), dried over magnesium sulphate and the solvent was removed *in vacuo* yielding the crude intermediate product. This was purified by column chromatography on a silica stationary phase using 3:1 diethylether:chloroform as the mobile phase to isolate the pure intermediate product.

The crude intermediate was then dissolved in 4:1 acetic acid:water mixture (100 mL). This was stirred at 40 ^oC and monitored by TLC every 10 minutes with 3:1 diethyl ether:chloroform. When the reaction had gone to completion it was quenched by the addition of saturated sodium carbonate until the acid was neutralised and dichloromethane to keep the product in solution. The solution was transferred to a separating funnel. The organic layer was extracted and washed with distilled water (50.0 mL X4), and saturated sodium bicarbonate solution (20.0 mL X4). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The product was

recrystallised from chloroform:hexane to isolate the pure product (68 %, 1.282 g, 2.92 mmol) as a colourless solid.

^{1}H NMR ($CDCl_3$): δ(ppm) 8.08 (4H, s, *H1*), 6.89-6.75 (8H, m, *H's 7,8, 9 and 10*), 4.66 (4H, t, *J* = 4.6 *Hz, H4*), 4.33 (4H, t, *J* = 4.4 *Hz, H5*)

^{13}C NMR ($CDCl_3$): δ(ppm) 165.77 (*3*), 146.15 (*C11*), 145.46 (*C6*), 133.70 (*C2*), 129.79 (*C1*), 122.47 (*C8*), 120.18 (*C9*), 115.09 (*C10*), 112.49 (*C7*), 67.49 (*C5*), 63.67 (*C4*).

IR (KBr disc): σ(cm^{-1}) 3436, 3288, 2953, 2926, 2362, 2340, 1732, 1605, 1507, 1458, 1408, 1261, 1181, 1100, 1072, 1014.

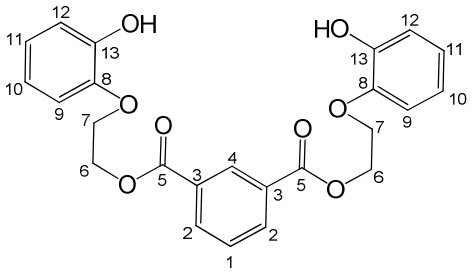
MP: 212-213 ^{o}C

Calculated exact mass for product: ($C_{24}H_{22}O_8$) 438.1315

Calculated exact mass for product + proton: ($C_{24}H_{22}O_8H^+$) 439.1387

Found: HRMS (EI, 70 eV) 439.1410

***Bis*(2-(2-Hydroxyphenoxy)ethyl)isophthalate, 355:**



2-(2-(Triethylsilyloxy)phenoxy)ethanol, **345**, (2.276 g, 8.4 mmol) was dissolved in dry dichloromethane (60.0 mL) at room temperature. Dry triethylamine (4.2 mL, 30 mmol) was added whilst stirring. Isophthaloyl dichloride (0.848 g, 4.2 mmol) was added slowly to the reaction mixture. The reaction mixture was stirred for 48 hours. The reaction was quenched by adding distilled water (20.0 mL) and stirring for ten minutes. The organic and aqueous layers were separated. The organic layer was washed with distilled water (20.0 mL X5), then dried over magnesium sulphate and the solvent was removed *in vacuo* yielding the crude intermediate product. This was purified by column chromatography on a silica stationary phase using 3:1 diethylether:chloroform as the mobile phase to isolate the pure intermediate product.

The intermediate was then dissolved in 4:1 acetic acid:water mixture (100 mL). This was then stirred at 40 ^{o}C and monitored by TLC every 10 minutes with a 3:1 diethylether:chloroform mobile phase. When the reaction had gone to completion it

was quenched by the addition of saturated sodium carbonate until the acid was neutralised and dichloromethane to keep the product in solution. The solution was transferred to a separating funnel. The organic layer was extracted and washed with distilled water (50.0 mL X4), and saturated sodium bicarbonate solution (20.0 mL X4). The organic layer was then dried over $MgSO_4$ and the solvent removed *in vacuo*. The product was recrystallised from chloroform:hexane to isolate the pure product (52 %, 0.982 g, 2.18 mmol) as a colourless solid.

^{1}H NMR ($CDCl_3$): δ(ppm) 8.63 (1H, t, *J* = 1.6 *Hz, H4*), 8.16 (2H, dd, *J* = 8.0, 1.6 *Hz, H2*), 7.46 (1H, t, *J* = 8.0 *Hz, H1*), 6.88-6.74 (8H, m*, H's 9, 10, 11 and 12*), 4.66 (4H, t, *J* = 4.4 *Hz, H6*), 4.32 (4H, t, *J* = 4.4 *Hz, H17*).

^{13}C NMR ($CDCl_3$): δ(ppm) 165.71 (*C5*), 146.15 (*C13*), 145.48 (*C8*), 134.29 (*C2*), 130.94 (*C4*), 130.22 (*C3*), 128.89 (*C1*), 122.40 (*C10*), 120.18 (*C11*), 115.09 (*C12*), 112.50 (*C9*), 67.51 (*C6*), 63.53 (*C7*).

IR (KBr disc): σ(cm^{-1}) 3452, 3074, 2942, 2882, 1737, 1605, 1501, 1452, 1304, 1268, 1276, 1102, 1052.

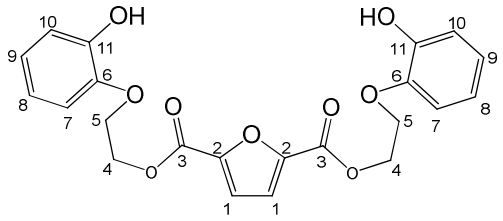
MP: 132-133 ^oC

Calculated exact mass for product: ($C_{24}H_{22}O_8$) 438.1315

Calculated exact mass for product + proton: ($C_{24}H_{22}O_8H^+$) 439.1387

Found: HRMS (EI, 70 eV) 439.1384

***Bis*(2-(2-hydroxyphenoxy)ethyl)furan-2,5-dicarboxylate, 356:**



2-(2-(Triethylsilyloxy)phenoxy)ethanol, **345**, (2.276 g, 8.4 mmol) was dissolved in dry dichloromethane (60.0 mL) at room temperature. Dry triethylamine (4.2 mL, 30 mmol) was added whilst stirring. Furan-2,5-dicarbonyl dichloride (0.655 g, 4.2 mmol) was added slowly to the reaction mixture. The reaction mixture was stirred for 48 hours. The reaction was quenched by adding distilled water (20.0 mL) and stirring for ten minutes. The organic and aqueous layers were separated. The organic layer was washed with distilled water (20.0 mL X5), dried over magnesium sulphate and the solvent was removed *in vacuo* yielding the crude intermediate product. This was

purified by column chromatography on a silica stationary phase using 3:1 diethylether:chloroform as the mobile phase to isolate the pure intermediate product.

The intermediate was dissolved in 4:1 acetic acid:water mixture (100 mL). This was stirred at 40 ^{o}C and monitored by TLC every 10 minutes with 3:1 diethylether:chloroform. When the reaction had gone to completion it was quenched by the addition of saturated sodium carbonate until the acid was neutralised and dichloromethane to keep the product in solution. The solution was transferred to a separating funnel. The organic layer was extracted and washed with distilled water (50.0 mL X4), and saturated sodium bicarbonate solution (20.0 mL X4). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The product was recrystallised from chloroform:hexane to isolate the pure product (61 %, 1.097 g, 2.56 mmol) as a colourless solid.

^{1}H NMR (DMSO-d_6): δ(ppm) 7.41 (2H, s, *H1*), 6.96 (2H, d, *J* = 7.6 *Hz, H8*), 6.79 (4H, dd, *J* = 4.3, 1.9 *Hz, H's 9 and 10*), 6.71-6.74 (2H, m, *H7*), 4.61, (4H, t, *J* = 4.5 *Hz, H4*), 4.29 (4H, t, *J* = 4.5 *Hz, H5*)

^{13}C NMR (DMSO-d_6): δ(ppm) 157.34 (*C3*), 147.09 (*C11*), 146.34 (*C2*), 146.06 (*C6*), 121.80 (*C8*), 119.29 (*C9*), 119.16 (*C1*), 115.89 (*C10*), 114.82 (*C7*), 66.67 (*C5*), 64.10 (*C4*).

IR (KBr disc): σ(cm^{-1}) 3397, 2937, 2877, 2361, 1742, 1605, 1501, 1458, 1380, 1336, 1309, 1291, 1264, 1221, 1169, 1131, 1111, 1069, 1045, 1035, 1004.

MP: 113-115 ^{o}C

Calculated exact mass for product: ($C_{22}H_{20}O_9$) 428.1107

Calculated exact mass for product + proton: ($C_{22}H_{20}O_9H^+$) 429.1180

Found: HRMS (EI, 70 eV) 429.1172

Synthesis of the 2-(2-hydroxyethoxy)phenol based macrocycles from the bis-phenols:

Synthesis of 2,3,6,9,11,12,13,19,22-tetrabenzo-1,4,11,14,17,24-hexaoxacyclohexa-icosa-2,6,8,12,19,21-hexaene-5,10,18,23-tetraone, 353:

Bis(2-(2-Hydroxyphenoxy)ethyl) terephthalate, **347**, (0.250 g, 0.571 mmol) was dissolved in dichloromethane (10.0 mL) under nitrogen at room temperature. Triethylamine (0.4 mL, 2.8 mmol) was added. Terephthaloyl dichloride (0.115 g, 0.571 mmol) was dissolved in dichloromethane (10.0 mL) and added slowly to the reaction mixture. This was stirred for sixteen hours. After this time had elapsed the reaction was quenched by adding distilled water (20.0 mL) and stirring for ten minutes. The reaction

mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X3), dried over magnesium sulphate and then the solvent was removed *in vacuo*. Recrystallisation from chloroform:hexane gave the pure product (7 %, 0.022 g, 0.040 mmol) as a colourless solid. 1H NMR, 13C NMR, MP and IR data matches that which is stated on page 120.

Synthesis of 2,3,6,7,10,11,17,20-tetrabenzo-1,4,9,12,15,22-hexaoxacyclotetraeicosa-2,6,10,17,19-pentaene-5,8,16,21-tetraone, 350:

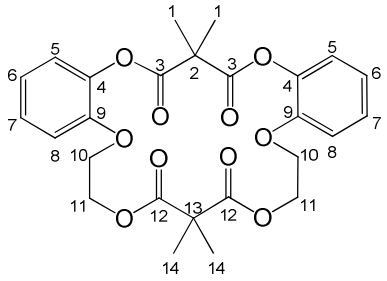
Bis(2-(2-Hydroxyphenoxy)ethyl) terephthalate, **347**, (0.250 g, 0.571 mmol) was dissolved in dichloromethane (10.0 mL) under nitrogen at room temperature. Triethylamine (0.4 mL, 2.8 mmol) was added. Phthaloyl dichloride (0.0814 mL, 0.571 mmol) was dissolved in dichloromethane (10.0 mL) and added slowly to the reaction mixture. This was stirred for sixteen hours. After this time had elapsed the reaction was quenched by adding distilled water (20.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X3), dried over magnesium sulphate and the solvent was removed *in vacuo*. Recrystallisation from chloroform:hexane gave the pure product (6 %, 19 mg, 0.034 mmol) as a colourless solid. ^{1}H NMR, ^{13}C NMR, MP and IR data matches that which is stated on page 116.

Synthesis of 2,3,6,8,11,12,18,21-tetrabenzo-1,4,10,13,16,23-hexaoxacyclopenta-icosa-2,6,11,18,20-pentaene-5,9,17,22-tetraone, 352:

Bis(2-(2-Hydroxyphenoxy)ethyl) terephthalate, **347**, (0.250 g, 0.571 mmol) was dissolved in dichloromethane (10.0 mL) under nitrogen at room temperature. Triethylamine (0.4 mL, 2.8 mmol) was added. Isophthaloyl dichloride (0.116 mg, 0.571 mmol) was dissolved in dichloromethane (10.0 mL) and added slowly to the reaction mixture. This was stirred for sixteen hours. After this time had elapsed the reaction was quenched by adding distilled water (20.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X3), dried over magnesium sulphate and the solvent was removed *in vacuo*. Recrystallisation from chloroform:hexane gave the pure product (3.1 %, 10 mg, 0.018

mmol) as a colourless solid. 1H NMR, 13C NMR, MP and IR data matches that which is stated on page 119.

Synthesis of 2,3,9,10-dibenzo-6,16-tetramethyl-1,4,8,11,14,18-hexaoxacyclohexa-icosa-2,9-diene-5,7,15,17-tetraone, 357:



Bis(2-(2-Hydroxyphenoxy)ethyl)-2,2-dimethylmalonate, **346**, (0.222 g, 0.54 mmol) was dissolved in dichloromethane (10.0 mL) under nitrogen at room temperature. To this triethylamine (0.4 mL, 2.8 mmol) was added. Dimethylmalonyl chloride (0.073 mL, 0.54 mmol) was dissolved in dichloromethane (10.0 mL) and added slowly to the reaction mixture. This was stirred for sixteen hours. After this time had elapsed the reaction was quenched by adding distilled water (20.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X3), dried over magnesium sulphate and the solvent was removed *in vacuo*. Recrystallisation from chloroform:hexane gave the pure product (25 %, 0.070 g, 0.14 mmol) as a colourless solid.

^{1}H NMR ($CDCl_3$): δ(ppm) 7.14-7.02 (8H, m, *H's 5 to 8*), 4.48 (4H, t, *J* = 4.4 *Hz, H11*), 4.05 (4H, t, *J* = 4.4 *Hz, H10*), 1.53 (12H, s, *H's 1 and 14*).

^{13}C NMR ($CDCl_3$): δ(ppm) 172.70 (*C12*), 170.81 (*C3*), 150.77 (*C9*), 142.82 (*C4*), 127.33 (*C7*), 124.69 (*C6*), 124.45 (*C5*), 123.25 (*C8*), 72.54 (*C11*), 64.03 (*C10*), 50.95 (*C's 2 and 13*), 20.96 (*C's 1 and 14*).

IR (KBr disc): σ(cm^{-1}) 3102, 3067, 3041, 2999, 2966, 2885, 2361, 1784, 1742, 1600, 1491, 1455, 1390, 1366, 1276, 1237, 1177, 1149, 1095, 1044, 1019.

MP: 126-128 ^{o}C

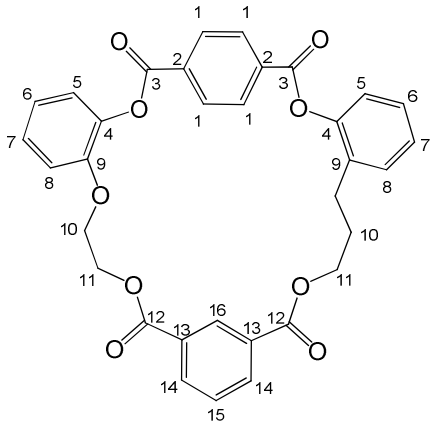
Calculated exact mass for product: ($C_{26}H_{28}O_{10}$) 500.1682

Calculated exact mass for product + proton: ($C_{26}H_{28}O_{10}H^{+}$) 501.1755

Found: HRMS (EI, 70 eV) 501.1761

One pot synthesis of the 2-(2-hydroxyethoxy)phenol based macrocycles:

Synthesis of 2,3,6,9,11,12,13,19,21-tetrabenzo-1,4,11,14,17,23-hexaoxacyclopenta-icosa-2,6,8,12,19-pentaene-5,10,18,22-tetraone, 358:



2-(2-Hydroxyethoxy)phenol (1.54 g, 10.0 mmol) was dissolved in dry dichloromethane (100 mL) at room temperature under nitrogen and chilled to -15^{o}C. At -15^{o}C dry triethylamine (5.0 mL, 36 mmol) was added with stirring. Terephthaloyl dichloride (1.005 g, 5.0 mmol) was dissolved in dry dichloromethane (25.0 mL) and added slowly to the reaction mixture. The reaction mixture was stirred for one hour at -15 ^{o}C. After this period had elapsed the reaction mixture was allowed to warm to room temperature and was stirred at room temperature for sixteen hours. Dry triethylamine (5.0 mL, 36 mmol) was added to the reaction flask. Isophthaloyl dichloride (1.005 g, 5.00 mmol) was dissolved in dry dichloromethane (300 mL) and added slowly to the reaction mixture. This reaction mixture was stirred for sixteen hours and then quenched by adding distilled water (50.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X6), dried over magnesium sulphate and the solvent was removed *in vacuo*. Column chromatography on a silica stationary phase with mobile phase of 3:1 ether:chloroform followed by recrystallisation from toluene gave the pure product (6 %, 0.170 g, 0.3 mmol) as a colourless solid.

^{1}H NMR ($CDCl_3$): δ(ppm) 8.14 (1H, br. s, *H16*), 8.13 (2H, dd, *J* = 8.7, 1.2 *Hz, H14*), 7.73 (4H, s, *H1*), 7.46 (1H, t, *J* = 8.2 *Hz, H5*), 7.21 (2H, td, *J* = 8.7, 1.2 *Hz, H15*), 7.12

(4H, dd, *J* = 6.9, 1.2 *Hz, H7*), 7.07 (4H, dd, *J* = 6.9, 1.2 *Hz, H6*), 6.99 (2H, td, *J* = 7.6, 1.2 *Hz, H8*), 4.53 (4H, t, *J* = 4.0 *Hz, H11*), 4.37 (4H, t, *J* = 4.0 *Hz, H10*).

^{13}C NMR ($CDCl_3$): δ(ppm) 165.31 (*C12*), 163.83 (*C3*), 149.65 (*C9*), 140.90 (*C4*), 133.91 (*C2*), 132.85 (*C14*), 130.43 (*C13*), 130.13 (*C1*), 129.67 (*C16*), 128.53 (*C15*), 127.16 (*C7*), 123.09 (*C6*), 122.08 (*C5*), 114.67 (*C8*), 66.91 (*C10*), 62.95 (*C11*).

IR (KBr disc): σ(cm^{-1}) 3069, 2967, 2878, 2364, 1728, 1607, 1589, 1501, 1457, 1435, 1407, 1375, 1310, 1262, 1229, 1186, 1114, 1088, 1058, 1015.

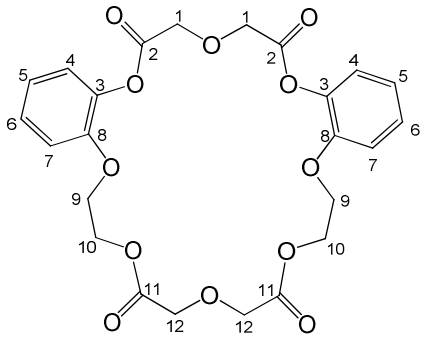
MP: 126-128 ^oC

Calculated exact mass for product: ($C_{32}H_{24}O_{10}$) 568.1369

Calculated exact mass for product + proton: ($C_{32}H_{24}O_{10}H^+$) 569.1442

Found: HRMS (EI, 70 eV) 569.1448

Synthesis of 2,3,11,12-dibenzo-1,4,7,10,13,16,19,22-octaoxacyclotetraeicosa-2,11-diene-5,9,17,21-tetraone, 359:



2-(2-Hydroxyethoxy)phenol (1.54 g, 10.0 mmol) was dissolved in dry dichloromethane (100 mL) at room temperature under nitrogen and chilled to -15^oC. At -15^oC dry triethylamine (5.0 mL, 36 mmol) was added with stirring. Diglycolyl chloride (0.855 g, 5.0 mmol) was dissolved in dry dichloromethane (25.0 mL) and added slowly to the reaction mixture. The reaction mixture was stirred for one hour at -15 ^oC. After this period had elapsed the reaction mixture was allowed to warm to room temperature and was stirred at room temperature for sixteen hours. Dry triethylamine (5.0 mL, 36 mmol) was added to the reaction flask. Diglycolyl chloride (0.855 g, 5.0 mmol) was dissolved in dry dichloromethane (300 mL) and added slowly to the reaction mixture. This reaction mixture was stirred for 24 hours and quenched by adding distilled water (50.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X6), dried over magnesium sulphate and the

solvent was removed *in vacuo*. Column chromatography on a silica stationary phase with mobile phase of 1:1 ethylacetate:chloroform yielded the pure product (7 %, 0.185 g, 0.35 mmol) as a colourless solid.

^{1}H NMR ($CDCl_3$): δ(ppm) 7.14 (2H, dt, *J* = 7.8, 1.7 *Hz, H4*), 7.01 (2H, dd, *J* = 7.9, 1.7 *Hz, H6*), 6.98 (2H, dt, *J* = 7.8, 1.3 *Hz, H5*), 6.86 (2H, dd, *J* = 7.9, 1.3 *Hz, H7*), 4.54 (4H, s, *H12*), 4.46 (4H, t, *J* = 4.1 *Hz, H10*), 4.30 (4H, s, *H1*), 4.12 (4H, t, *J* = 4.1 *Hz, H9*)

^{13}C NMR ($CDCl_3$): δ(ppm) 169.00 (*C11*), 166.58 (*C2*), 148.56 (*C8*), 138.30 (*C3*), 126.20 (*C6*), 121.69 (*C4*), 120.46 (*C5*), 111.97 (*C7*), 67.15 (*C12*), 67.08 (*C1*), 65.44 (*C10*), 61.29 (*C9*).

IR (KBr disc): σ(cm^{-1}) 3065, 3039, 2968, 2931, 2364, 1741, 1607, 1503, 1452, 1410, 1378, 1285, 1261, 1178, 1145, 1041, 984, 953, 911, 820, 779, 742, 602.

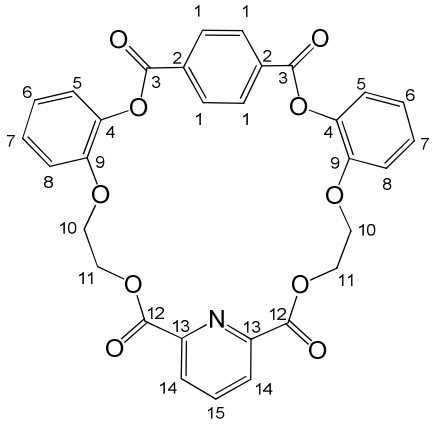
MP: 97-99 ^{o}C

Calculated exact mass for product: ($C_{22}H_{24}O_{12}$) 504.1268

Calculated exact mass for product + sodium: ($C_{24}H_{24}O_{12}Na^{+}$) 527.1160

Found: HRMS (EI, 70 eV) 527.1165

Synthesis of 2,3,6,9,12,13,19,21-tetrabenzo-20-aza-1,4,11,14,17,23-hexaoxacyclo-pentaicosa-2,6,8,12,19-pentaene-5,10,18,22-tetraone, 360:



2-(2-Hydroxyethoxy)phenol (0.308 g, 2.00 mmol) was dissolved in dry dichloromethane (20 mL) at room temperature under nitrogen and chilled to -15 ^{o}C. Once the temperature had reached -15 ^{o}C dry triethylamine (0.7 mL, 5.0 mmol) was added with stirring. Terephthaloyl dichloride (203 mg, 1.00 mmol) was dissolved in dry dichloromethane (20.0 mL) and added slowly to the reaction mixture. The reaction mixture was stirred for one hour at -15 ^{o}C. After this period had elapsed the reaction mixture was allowed to warm to room temperature and was stirred at room temperature

for sixteen hours. Dry triethylamine (0.7 mL, 5.0 mmol) was added to the reaction flask. Pyridine-2,6-dicarbonyl dichloride (204 mg, 1.00 mmol) was dissolved in dry dichloromethane (260 mL) and added slowly to the reaction mixture. This reaction mixture was stirred for 24 hours and then quenched by adding distilled water (50.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X6), dried over magnesium sulphate and the solvent was removed *in vacuo*. Column chromatography on a silica stationary phase with mobile phase of 4:1 diethyl ether:dichloromethane yielded the pure product (6 %, 0.034 g, 0.06 mmol) as a colourless solid.

^{1}H NMR ($CDCl_3$): δ(ppm) 8.14 (2H, d, *J* = 7.8 *Hz, H14*), 7.91 (1H, t, *J* = 7.8 *Hz, H15*), 7.70 (4H, s, *H1*), 7.21 (2H, td, *J* = 8.2 *Hz,* 1.7 *Hz, H5*), 7.08 (2H, dd, *J* = 7.8*,* 1.7 *Hz, H7*), 7.04 (4H, dd, *J* = 8.2*,* 1.2 *Hz, H6*), 6.99 (2H, td, *J* = 7.8 *Hz,* 1.2 *Hz, H8*), 4.58 (4H, t, *J* = 4.2 *Hz, H11*), 4.39 (4H, t, *J* = 4.2 *Hz, H10*).

^{13}C NMR ($CDCl_3$): δ(ppm) 163.90 (*C's 3 and 12*), 149.60 (*C9*), 148.04 (*C13*), 140.90 (*C2*), 137.95 (*C15*), 132.91 (*C4*), 129.63 (*C1*), 127.84 (*C*14), 127.18 (*C7*), 123.06 (*C6*), 122.12 (*C5*), 114.76 (*C8*), 66.60 (*C10*), 63.71 (*C11*).

IR (KBr disc): σ(cm^{-1}) 2961, 2365, 2345, 1746, 1722, 1606, 1498, 1317, 1284, 1263, 1247, 1181, 1146, 1110, 1063, 1016.

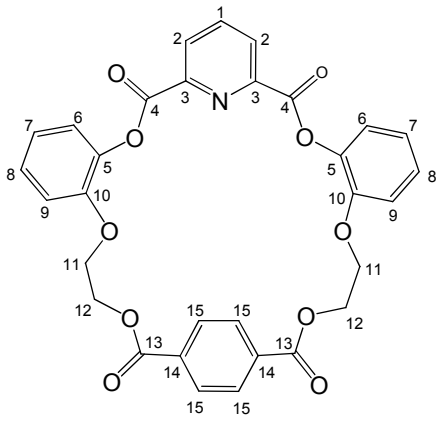
MP: 226-227 ^{o}C

Calculated exact mass for product: ($C_{31}H_{23}NO_{10}$) 569.1322.

Calculated exact mass for product + proton: ($C_{31}H_{23}NO_{10}H^{+}$) 570.1395

Found: HRMS (EI, 70 eV) 570.1400

Synthesis of 2,3,6,8,11,12,18,21-tetrabenzo-7-aza-1,4,10,13,16,23-hexaoxacyclo-pentaicosa-2,6,11,18,20-pentaene-5,9,17,21-tetraone, 361:



2-(2-Hydroxyethoxy)phenol (0.308 g, 2.00 mmol) was dissolved in dry dichloromethane (20 mL) at room temperature under nitrogen and chilled to -15 ^{o}C. Dry triethylamine (0.7 mL, 5.0 mmol) was added with stirring. Pyridine-2,6-dicarbonyl dichloride (204 mg, 1.00 mmol) was dissolved in dry dichloromethane (20.0 mL) and added slowly to the reaction mixture. The reaction mixture was stirred for one hour at -15 ^{o}C. After this period had elapsed the reaction mixture was allowed to warm to room temperature and was stirred at room temperature for sixteen hours. Dry triethylamine (0.7 mL, 5.0 mmol) was added to the reaction flask. Terephthaloyl dichloride (203 mg, 1.00 mmol) was dissolved in dry dichloromethane (260 mL) and added slowly to the reaction mixture. This reaction mixture was stirred for 24 hours and quenched by adding distilled water (50.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X6), dried over magnesium sulphate and then the solvent was removed *in vacuo*. Column chromatography on a silica stationary phase with mobile phase of 4:1 diethyl ether:dichloromethane yielded the pure product (3.5 %, 0.020 g, 0.035 mmol) as a colourless solid. Due to the low solubility of this product in all available solvents a ^{13}C NMR could not be recorded. There was not enough isolated product to record the melting point.

^{1}H NMR (ACN-d_3): δ(ppm) 8.28 (2H, dd, *J* = 7.2, 1.8 *Hz, H2*), 8.03-7.97 (5H, m, *H's 15 and 1*), 7.34 (2H, td, *J* = 7.9, 1.6 *Hz, H7*), 7.20 (4H, dd, *J* = 7.8, 1.5 *Hz, H's 6 and 8*), 7.08 (2H, td, *J* = 7.7, 1.4 *Hz, H9*), 4.60 (4H, t, *J* = 4.3 *Hz, H12*), 4.40 (4H, t, *J* = 4.3 *Hz, H11*).

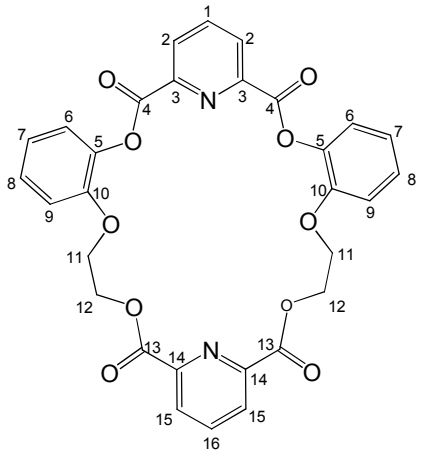
IR (KBr disc): σ(cm^{-1}) 3449, 2366, 2346, 1754, 1718, 1686, 1500, 1458, 1315, 1287, 1236, 1185, 1138, 1162, 1111.

Calculated exact mass for product: ($C_{31}H_{23}NO_{10}$) 569.1322.

Calculated exact mass for product + proton: ($C_{31}H_{23}NO_{10}H^+$) 570.1395

Found: HRMS (EI, 70 eV) 570.1400

Synthesis of 2,3,6,8,11,12,18,20-tetrabenzo-7,19-diaza-1,4,10,13,16,22-hexaoxa-cyclotetraicosa-2,6,11,18-tetraene-5,9,17,21-tetraone, 362:



2-(2-Hydroxyethoxy)phenol (0.308 g, 2.00 mmol) was dissolved in dry dichloromethane (20 mL) at room temperature under nitrogen and chilled to -15 ^oC. Dry potassium carbonate (1.2 g) was added with stirring. Pyridine-2,6-dicarbonyl dichloride (204 mg, 1.00 mmol) was dissolved in dry dichloromethane (20.0 mL) and added slowly to the reaction mixture. The reaction mixture was stirred for one hour at -15 ^oC. After this period had elapsed the reaction mixture was allowed to warm to room temperature and was stirred at room temperature for sixteen hours. Dry potassium carbonate (1.2 g) was added to the reaction flask. Pyridine-2,6-dicarbonyl dichloride (204 mg, 1.00 mmol) was dissolved in dry dichloromethane (260 mL) and added slowly to the reaction mixture. This reaction mixture was stirred for 24 hours and then quenched by adding distilled water (50.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X6), dried over magnesium sulphate and the solvent was removed *in vacuo*. Recrystallisation from $CHCl_3$ gave the pure product (14 %, 80 mg, 0.14 mmol) as a colourless solid.

^1H NMR (ACN-d_3): δ(ppm) 8.25 (2H, d, *J* = 7.6 *Hz, H2*), 8.18 (2H, d, *J* = 8.0 *Hz, H15*), 8.02 (1H, t, *J* = 7.6 *Hz, H1*), 7.97 (1H, t, *J* = 8.0 *Hz, H16*), 7.34 (2H, dt, *J* = 7.7,

1.6 *Hz, H6*), 7.23 (4H, dt, *J* = 7.9*,* 1.4 *Hz, H8*), 7.22 (4H, dt, *J* = 7.9*,* 1.6 *Hz, H7*), 7.08 (2H, dt, *J* = 7.7*,* 1.4 *Hz, H9*), 4.69 (4H, t, *J* = 4.2 *Hz, H12*), 4.42 (4H, t, *J* = 4.2 *Hz, H11*).

^{13}C NMR (ACN-d_3): δ(ppm) 163.83 (*C*13), 162.17 (*C4*), 149.73 (*C10*), 147.38 (*C14*), 146.83 (*C3*), 139.98 (*C16*), 138.61 (*C1*), 138.30 (*C5*), 128.48 (*C15*), 127.91 (*C2*), 127.18 (*C8*), 122.54 (*C7*), 121.29 (*C6*), 114.09 (*C9*), 66.70 (*C11*), 63.48 (*C12*).

IR (KBr disc): σ(cm^{-1}) 3407, 3105, 2966, 2885, 2366, 1755, 1734, 1717, 1630, 1608, 1584, 1504, 1458, 1403, 1378, 1316, 1285, 1235, 1186, 1164, 1113, 1077, 1063.

MP: 257-258 ^{o}C (at 245 ^{o}C turned from colourless solid to brown solid)

Calculated exact mass for product: ($C_{30}H_{22}N2O_{10}$) 570.1274

Calculated exact mass for product + proton: ($C_{31}H_{23}NO_{10}H^{+}$) 571.1347

Found: HRMS (EI, 70 eV) 571.1334

Synthesis of 2,3,6,8,11,12,18,20-tetrabenzo-1,4,10,13,16,22-hexaoxacyclotetra-icosa-2,6,11,18-tetraene-5,9,17,21-tetraone, 351:

2-(2-Hydroxyethoxy)phenol (0.462 g, 3.0 mmol) was dissolved in dry dichloromethane (20 mL) at room temperature under nitrogen and chilled to -15 ^{o}C. Dry triethylamine (1.5 mL, 11 mmol) was added with stirring. Isophthaloyl dichloride (304 mg, 1.5 mmol) was dissolved in dry dichloromethane (20.0 mL) and added slowly to the reaction mixture. The reaction mixture was then stirred for one hour at -15 ^{o}C. After this period had elapsed the reaction mixture was allowed to warm to room temperature and was stirred at room temperature for sixteen hours. Dry triethylamine (1.5 mL, 11 mmol) was added to the reaction flask. Isophthaloyl dichloride (304 mg, 1.5 mmol) was dissolved in dry dichloromethane (340 mL) and added slowly to the reaction mixture. This reaction mixture was stirred for 24 hours and then quenched by adding distilled water (50.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X6), dried over magnesium sulphate and the solvent was removed *in vacuo*. Column chromatography on a silica stationary phase with mobile phase of 3:1 diethyl ether:chloroform yielded the pure product (23 %, 0.199 g, 0.234 mmol) as a colourless solid. 1H NMR, 13C NMR, MP and IR data matches that which is stated on page 118.

Synthesis of 2,3,6,8,11,12,18,21-tetrabenzo-1,4,10,13,16,23-hexaoxacyclopentaicosa-2,6,11,18,20-pentaene-5,9,17,22-tetraone, 352:

2-(2-Hydroxyethoxy)phenol (1.54 g, 10.0 mmol) was dissolved in dry dichloromethane (100 mL) at room temperature under nitrogen and chilled to -15 ^{o}C. Dry triethylamine (5.0 mL, 36 mmol) was added with stirring. Isophthaloyl dichloride (1.005 g, 5.0 mmol) was dissolved in dry dichloromethane (25.0 mL) and added slowly to the reaction mixture. The reaction mixture was then stirred for one hour at -15 ^{o}C. After this period had elapsed the reaction mixture was allowed to warm to room temperature and was stirred at room temperature for sixteen hours. Dry triethylamine (5.0 mL, 36 mmol) was added to the reaction flask. Terephthaloyl dichloride (1.005 g, 5.0 mmol) was dissolved in dry dichloromethane (340 mL) and added slowly to the reaction mixture. This reaction mixture was stirred for 24 hours and then quenched by adding distilled water (50.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X6), dried over magnesium sulphate and the solvent was removed *in vacuo*. Column chromatography on a silica stationary phase 3:1 diethylether:chloroform followed by recrystallisation from diethylether:chloroform gave the pure product (14 %, 0.078 g, 0.7 mmol) as a colourless solid. 1H NMR, 13C NMR, MP and IR data matches that which is stated on page 119.

Synthesis of 2,3,6,9,11,12,13,19,22-tetrabenzo-1,4,11,14,17,24-hexaoxacyclohexaicosa-2,6,8,12,19,21-hexaene-5,10,18,23-tetraone, 353:

2-(2-Hydroxyethoxy)phenol (1.54 g, 10.0 mmol) was dissolved in dry dichloromethane (100 mL) at room temperature under nitrogen and chilled to -15 ^{o}C. Dry triethylamine (5.0 mL, 36 mmol) was added with stirring. Terephthaloyl dichloride (1.005 g, 5 mmol) was dissolved in dry dichloromethane (25.0 mL) and added slowly to the reaction mixture. The reaction mixture was stirred for one hour at -15 ^{o}C. After this period had elapsed the reaction mixture was allowed to warm to room temperature and was stirred at room temperature for sixteen hours. Dry triethylamine (5.0 mL, 36 mmol) was added to the reaction flask. Terephthaloyl dichloride (1.005 g, 5.0 mmol) was dissolved in dry dichloromethane (340 mL) and added slowly to the reaction mixture. This reaction mixture was stirred for 24 hours and then quenched by adding distilled water (50.0 mL) and stirring for ten minutes. The reaction mixture was

transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X6), dried over magnesium sulphate and then the solvent was removed *in vacuo*. Column chromatography on a silica stationary phase 3:1 ether:chloroform followed by recrystallisation from toluene gave the pure product (2.5 %, 14 mg, 0.12 mmol) as a colourless solid. 1H NMR, 13C NMR, MP and IR data matches that which is stated on page 120.

Synthesis of 2,3,11,12,-dibenzo-6,8,18,20-difurano-1,4,7,10,13,16,19,22-octaoxa-cyclohexaicosa-2,11-diaene-5,9,17,21-tetraone, 354:

2-(2-Hydroxyethoxy)phenol (0.308 g, 2.00 mmol) was dissolved in dry dichloromethane (10.0 mL) at room temperature under nitrogen and chilled to -15 ^{o}C. Dry triethylamine (1.0 mL, 7.2 mmol) was added with stirring. Furan-2,5-dicarbonyl dichloride (0.193 g, 1.00 mmol) was dissolved in dry dichloromethane (25.0 mL) and added slowly to the reaction mixture. The reaction mixture was stirred for one hour at -15 ^{o}C. After this period had elapsed the reaction mixture was allowed to warm to room temperature and was stirred at room temperature for sixteen hours. Dry triethylamine (1.0 mL, 7.2 mmol) was added to the reaction flask. Furan-2,5-dicarbonyl dichloride (0.193 g, 1.00 mmol) was dissolved in dry dichloromethane (120 mL) and added slowly to the reaction mixture. This reaction mixture was stirred for 24 hours and quenched by adding distilled water (50.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X6), dried over magnesium sulphate and the solvent was removed *in vacuo*. Column chromatography on a silica stationary phase dichloromethane followed by recrystallisation from chloroform:hexane gave the pure product (9 %, 0.049 g, 0.09 mmol) as a colourless solid. 1H NMR, 13C NMR, MP and IR data matches that which is stated on page 121.

Synthesis of 2,3,9,10-dibenzo-6,16-tetramethyl-1,4,8,11,14,18-hexaoxacyclo-hexaicosa-2,9-diene-5,7,15,17-tetraone, 357:

2-(2-Hydroxyethoxy)phenol (1.54 g, 10.0 mmol) was dissolved in dry dichloromethane (100 mL) at room temperature under nitrogen and chilled to -15 ^{o}C. Dry triethylamine (5.0 mL, 36 mmol) was added with stirring. Dimethylmalonyl chloride (0.845 g, 5 mmol) was dissolved in dry dichloromethane (25.0 mL) and added

slowly to the reaction mixture. The reaction mixture was stirred for one hour at -15 ^{o}C. After this period had elapsed the reaction mixture was allowed to warm to room temperature and was stirred at room temperature for sixteen hours. Dry triethylamine (5.0 mL, 36 mmol) was added to the reaction flask. Dimethylmalonyl chloride (0.845 g, 5.0 mmol) was dissolved in dry dichloromethane (300 mL) and added slowly to the reaction mixture. This reaction mixture was stirred for sixteen hours and then quenched by adding distilled water (50.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X6), dried over magnesium sulphate and the solvent was removed *in vacuo*. The crude product was a viscous liquid and with the addition of 3:1 ether:chloroform (20.0 mL) the product was isolated (2.5 %, 0.057 g, 0.12 mmol) as a colourless solid. 1H NMR, 13C NMR, MP and IR data matches that which is stated on page 130.

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Chapter 3:

Attempted Synthesis of the Macrocyclic Compounds Containing Morphine and the synthesis of precursors to these macrocycles

3.1 Introduction:

This chapter details the synthesis of five phenol linked morphine open structures and the attempted synthesis of two more phenol linked morphine open structures. The details of the attempted synthesis of twenty one macrocycles containing morphine are also discussed.

The main reasons for the study of synthetic methods of macrocycles containing morphine was to assist the long term goals of the Gathergood group; the development of chiral ligands for asymmetric synthesis, ion sensors and development of novel therapeutics.

The concept is to bind a chiral ligand to metals that had proven ability to act as catalysts, e.g. copper(II)[69], then use this metal bound species as a catalyst and as the ligand is chiral it may direct the reaction towards one enantiomer over the other. The chiral macrocycles being investigated in this chapter are under investigation for use as potential chiral ligands which can then be used in asymmetric synthesis. Although morphine has well known biological activity,[70] the reason it was chosen as a scaffold for chiral catalyst design and host guest studies was its rigid three dimensional structure. The rigid structure would then increase the likelihood of preferential binding of chiral guests. Also the rigid chiral structure may induce enantioselectivity to the products in any potential catalysed reactions. This would be done by carrying out binding studies, with various metals of interest from a catalytic perspective, to the macrocycles. Each of the macrocycles that bind effectively to the metals could then be tested in an established reaction making a chiral product to see if the macrocycle has an effect on the outcome of the reaction, i.e. increases the enantiomeric excess of either the *R* or *S* enantiomer.

The study of novel opiate products, including examples synthesised in this project, as potential analgesic therapeutics is also being carried out within the research group. This work is being undertaken as part of another project and will not be reported on in this thesis.

Each of the phenol linked morphine open structures were synthesised for use in the synthesis of morphine macrocycles. Metal binding studies were carried out on each of the successfully synthesised and isolated phenol linked morphine open structures with a variety of metal ions, the results of which will be discussed in chapter four.

The optimised method developed in chapter two for the synthesis of compound **353** is used in the study of the synthesis of the analogous macrocycle containing morphine and then other methods were tried to isolate this macrocycle.

The methods used for the investigation into another twenty macrocycles are also detailed.

The rigidity of the morphine molecule compared to the diol model was thought to be a limitation in the macrocyclisation reactions. As one of the aims of this project was to prepare the morphine macrocycles the size of the ring was varied in attempts to establish if any ring size was especially favourable to the cyclisation. Also the linker was varied to include both rigid and flexible linkers to test the effect of these on the macrocyclisation reactions. This approach meant the attempted synthesis of many different morphine macrocycle targets to try to establish if one macrocycle was more favourable.

3.2: Synthesis of phenol linked Morphine open structures

Five open structures (**368**-**372**) were successfully isolated and characterised. Attempts were made to synthesise and isolate two more open structures (**373** and **374**) but all these attempts were unsuccessful. The structures of these seven compounds are given in figure 80.

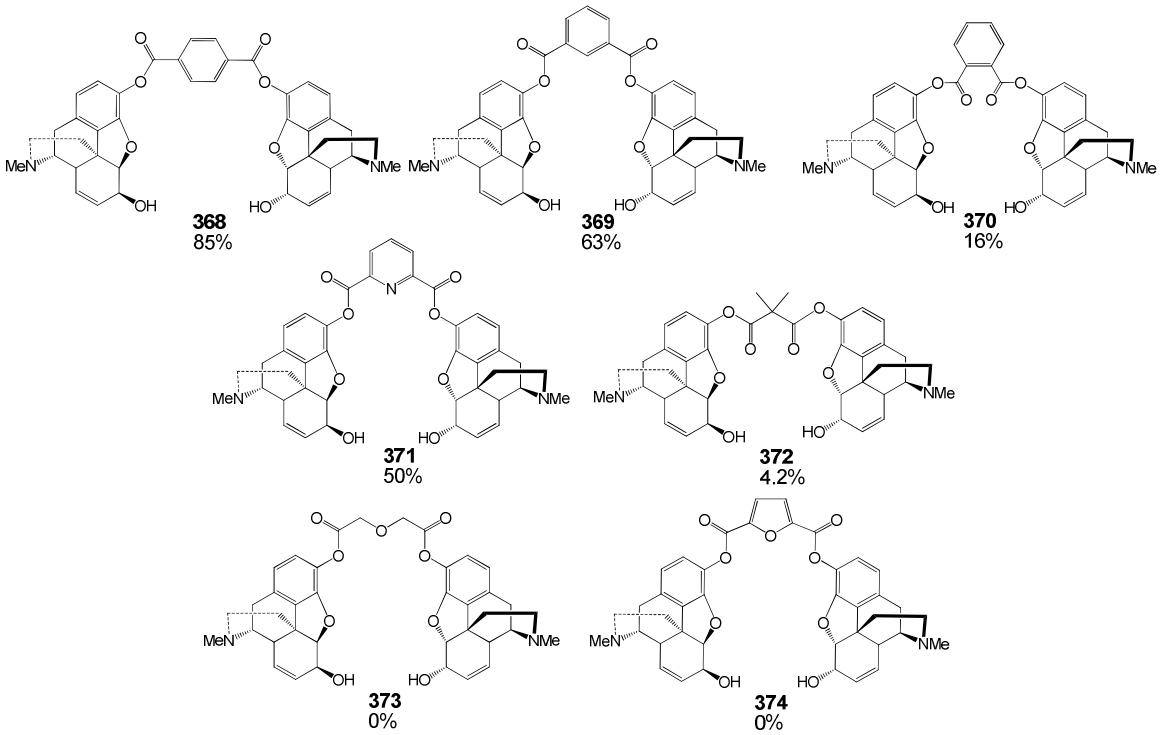
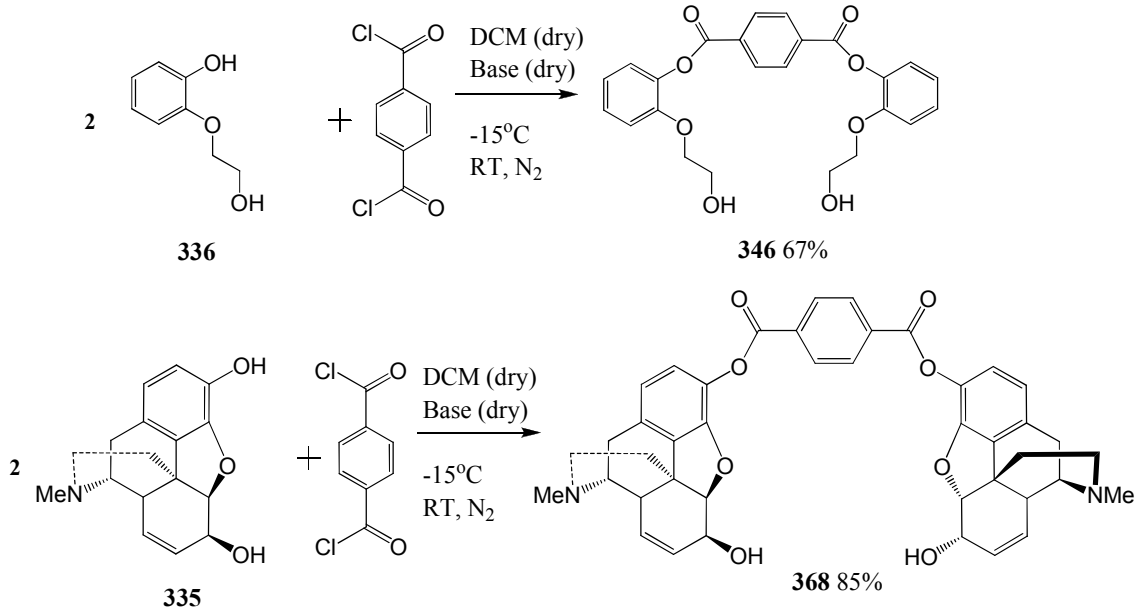


Figure 80: Compounds **368** *to* **374**

368-**372** were successfully synthesised by the same methodology, with the exception of the synthesis of **371** in which potassium carbonate was used instead of triethylamine. This method was the same as used for the synthesis of the analogous structures with 2-(2-hydroxyethoxy)phenol and an example of this, the synthesis of **368** and **346**, is shown in scheme 31.



Scheme 31: Synthesis of **346** *and* **368**

The methodology successfully produced **368**-**372**. In this method, in chapter 2, it has been shown that the acid chloride preferentially reacts with the phenol over the

aliphatic alcohol creating the target product. The *bis*-alcohol products in chapter 2 (**338**-**344**) did not undergo transesterification to create isomers. Although the reactivity of the alcohol groups will be different in morphine compared to the model (2-(2-hydroxyethoxy)phenol) the two alcohol groups should react in the same preferential order. This should lead to the selective synthesis of the target products over their isomers, e.g. **368** over **397**. Also if **368** is successfully synthesised then the likelihood of intermolecular transesterification is reduced because of the bulkiness and rigidity of the morphine moiety.

Also Mignat *et al.*[71] have synthesised ten morphine derivatives, all of which have been modified by esterification at the phenol. Each of these modified opiates have remarkably similar ^{1}H-NMR spectra and each of these are also similar to the recorded NMR data for the compounds **368**-**372**. The NMR data was similar for both the aromatic hydrogens (hydrogens on the A-ring) and also the hydrogens on the C-ring, ring labels shown in figure 81 below.

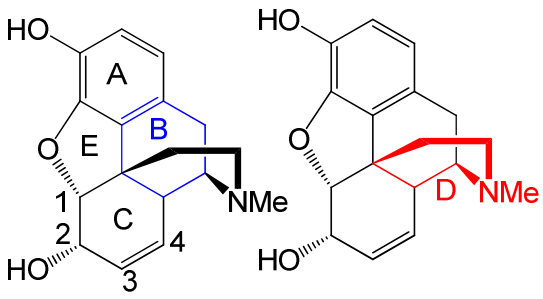


Figure 81: Ring labels of morphine

Although a lot of the other hydrogens also appear very similar the hydrogens of the A and C rings are the pivotal hydrogens for the differentiation of the possible isomers, those linked between the phenol groups and those linked between the aliphatic alcohols. If there is an ester formed on the aliphatic alcohols the hydrogens on rings A and C will be significantly different to the hydrogens in the same positions if the ester is on the phenol groups. This can be seen by the comparison of the recorded NMR data to that of 6-*O*-acetylmorphine reported by Schwarzinger *et al.*[72] For each of the products isolated in this section of the project H1 (as shown in figure 81) appears at 4.8 ppm with variation of approximately 0.1 ppm depending on the ester in the product, H2 at about 4.1 ppm, H3 at 5.7 ppm and H4 at 5.1 ppm, each with similar variation. This closely matches that which was by Mignat *et al.* whereas the reported NMR for 6-*O*-acetylmorphine by Schwarzinger *et al.* is significantly different showing the same hydrogens at 5.1 ppm for both H1 and H2, 5.4 ppm for H3 and 5.7 ppm for H4.

368, **369** and **371** were each isolated directly from the reaction in yields of 85 %, 63 % and 50 % respectively. **370** needed recrystallisation for purification and was isolated in 16 %. **372** required purification by column chromatography, and was isolated in a lower yield (4.2 %) than those successfully isolated with the aromatic diacid dichlorides.

373 and **374** (figure 80) were not successfully isolated. On the first attempt **373** was obtained with sufficient purity to record proton and carbon NMR spectra, this data is consistent with the structure of **373**. This suggests that with some further work this compound can be isolated. There were five further attempts to prepare and isolate compound **373**. The synthesis appeared to work on the first of these attempts with isolation failing, so the synthesis was repeated twice using the same method and different methods were attempted for isolation of the product. On the second attempt the aqueous layer was basified by the addition of saturated sodium hydroxide solution (2.0 mL). This was done in an attempt to force the product out of solution by ensuring that the nitrogen atoms in the opiate subunits were not protonated. The solution was then extracted with chloroform and both aqueous and organic layers were tested by NMR. It was found that the target product remained in the aqueous layer. Additional portions of saturated sodium hydroxide solution (2.0 mL) were added and after each addition the aqueous extracted with chloroform and both fractions were tested by NMR again. This was done until the product in the aqueous layer was seen to have degraded back to the starting material. On the final attempt using this method no water was added to quench or wash the reaction. The reaction was dried on the rotary evaporator without work up. Attempts were then made to purify this by recrystallisation, development of mobile phase for column chromatography, solid-liquid extractions and liquid-liquid extractions. All attempts were unsuccessful. The next attempt at the synthesis and isolation was carried out by refluxing in dichloromethane overnight, with the idea that as increased would lead to an easier isolation. This did not work, with a decreased yield being recorded by ^{1}H-NMR and attempts to isolate the product pure failed. The final attempt to synthesise and isolate compound **373** was done with dimethylaminopyridine instead of triethylamine. The reason for this was that in the reaction which had no water added the main impurity which could not be separated from the target product was the hydrochloride salt of triethylamine. With the change in base it was intended that this would be avoided. In the ^{1}H-NMR spectrum of the crude

product of this reaction it was found that the reaction did not work and therefore purification was not attempted.

The last open structure of this group at which attempts were made at the synthesis of was compound **374**. There were four attempts at the synthesis of compound **374**. All attempts at the synthesis of **374** were unsuccessful. The first two attempts were the same as the method that was used for each compound **368**-**372** with varying attempts at purification, including recrystallisation, using single solvents and solvent mixes, solid-liquid extraction, column chromatography and attempts at vacuum distillation. Then two attempts by the same method but varying the base were made, one with dimethylaminopyridine as base and one with potassium carbonate as base. No reaction took place in these two attempts at the synthesis and the starting material was recovered.

3.3: Attempted synthesis of the morphine containing macrocycles.

There were twenty one macrocycles containing morphine at which attempts were made at the synthesis and isolation. These are comprised of thirteen macrocycles analogous to the macrocycles in chapter 2 with morphine in place of 2-(2-hydroxyethoxy)phenol, shown in figure 82, and eight others which combined the aromatic linkers with aliphatic linkers, shown in figure 83 (page 156).

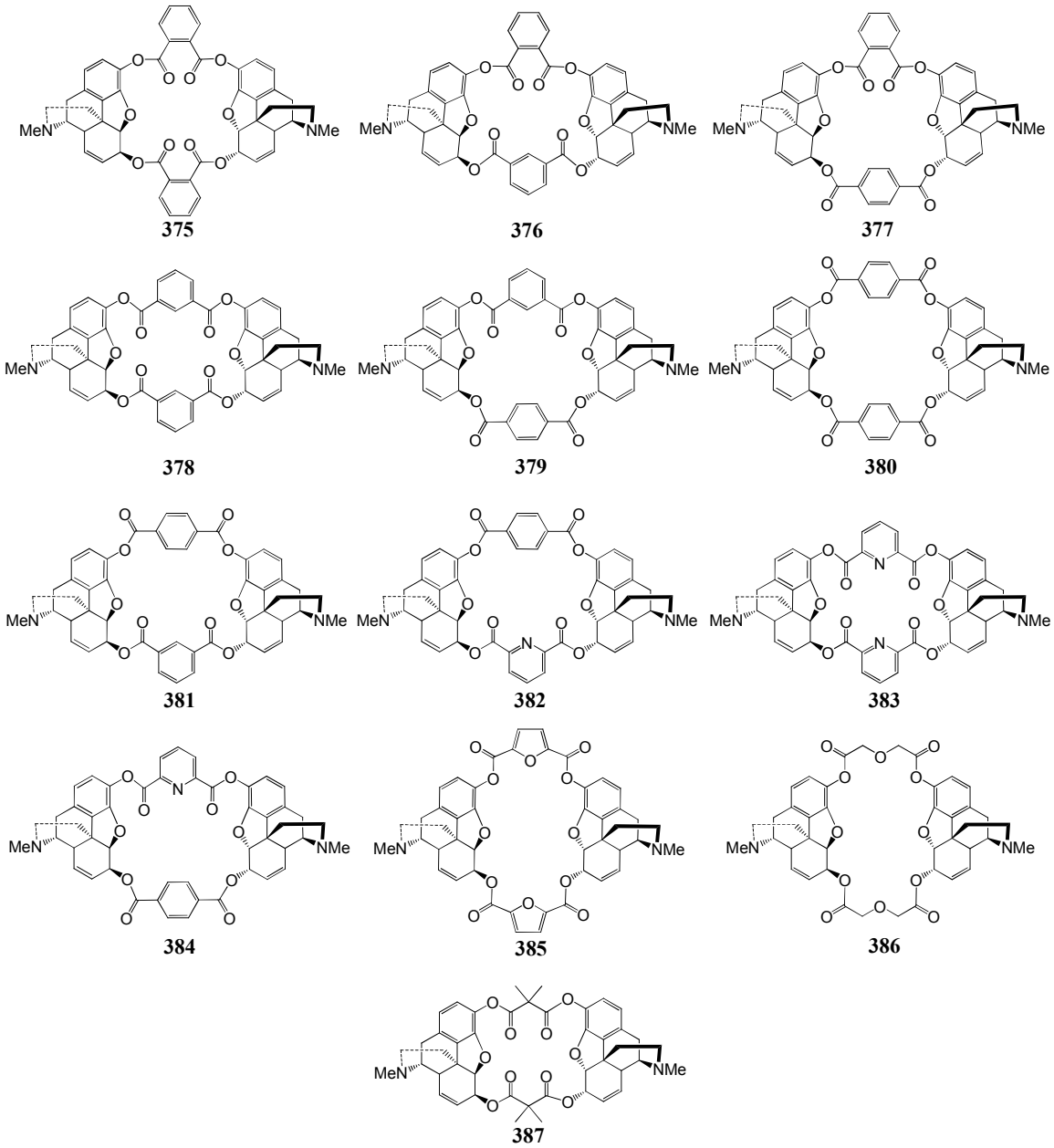


Figure 82: Compounds **375**-**387,** *the analogous macrocycles to those in chapter 2 which were not successfully isolated*

380 had the most attempts made at its synthesis as this was the macrocycle for which the analogous synthesis using the 2-(2-hydroxyethoxy)phenol was optimised. There were nineteen different methods used in the attempted synthesis and isolation of compound **380**. On the first attempt using the method directly from the optimisation of the synthesis of **290** from chapter two there appeared to be product present by NMR (NMR spectra are shown in figure 84 and 85).

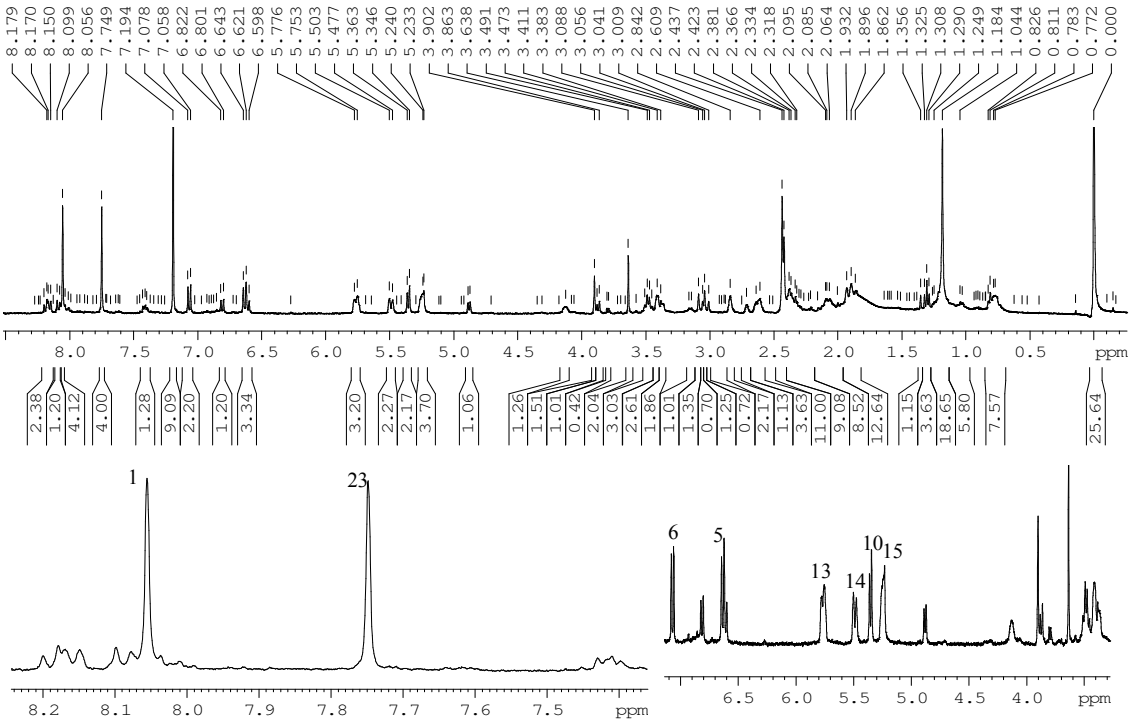


Figure 84: [1]H-NMR of compound **380**

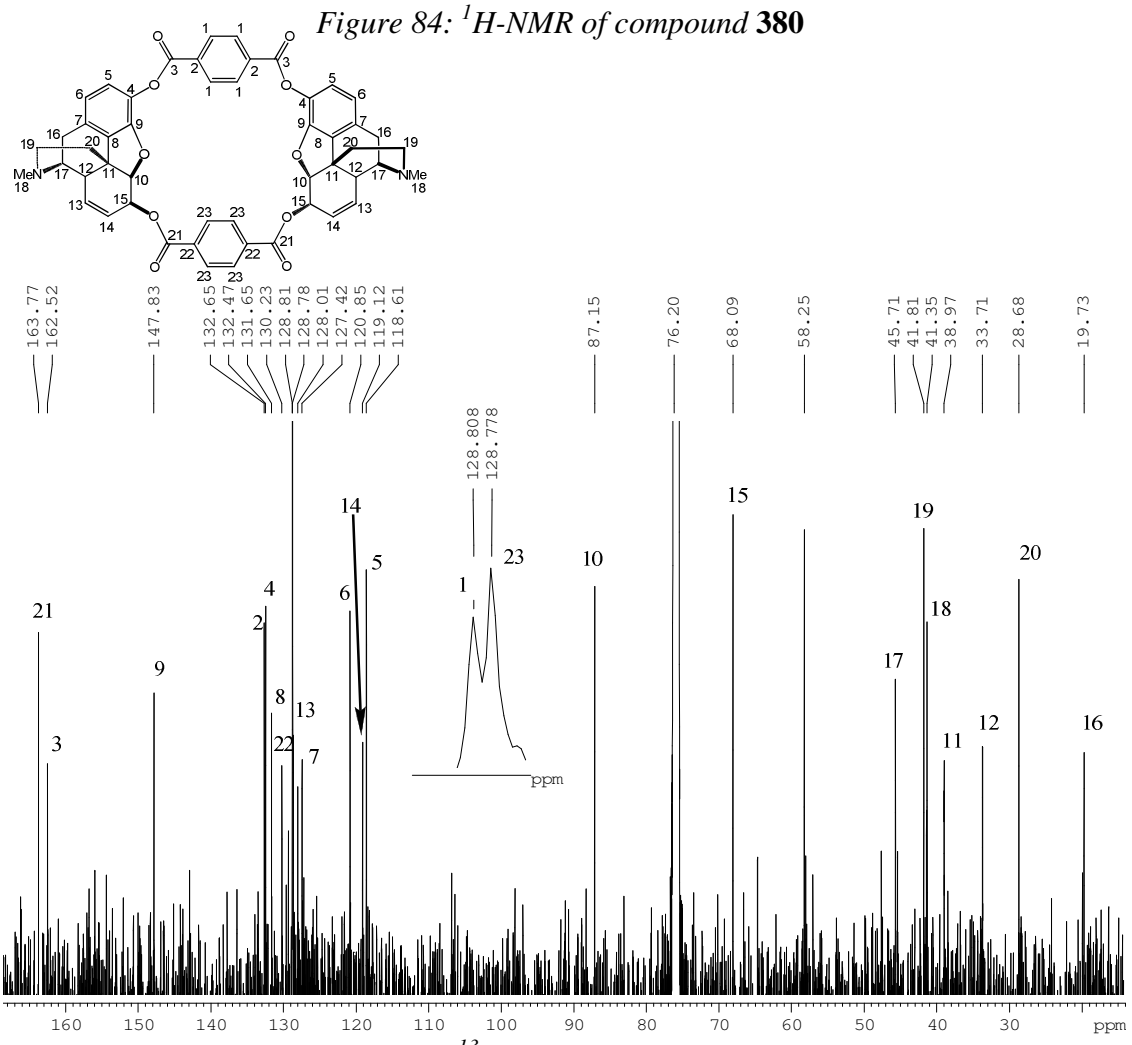


Figure 85: [13]C-NMR of compound **380**

In the proton NMR there can be clearly seen two singlets at 7.75 and 8.06 which have equal integral values. These peaks have a series of peaks throughout the spectrum which are in the correct regions for the morphine units expected in the macrocycle and these each have integral values matching the expected values. The product appears to be approximately 66 % pure by ^{1}H-NMR, with the peaks thought to be from the product having an integration of 2 and the impurity having an integration of 1.

The correct amount of peaks exist in the ^{13}C-NMR for the macrocycle and these peaks appear in the correct regions of the spectrum. There are two very similar peaks, at 128.79 and 128.81 at a stronger intensity than those around them, suggesting there are more carbon atoms for each of these peaks than for the surrounding peaks. This would be an expected if there are two terephthaloyl groups as in the proposed structure **380**.

The mass spectrum, IR spectrum, melting point and optical rotation were not recorded as it was intended to do this on the product once isolated pure and the attempted purification was not successful resulting in the loss of the target product.

380 was not isolated pure and it cannot be determined absolutely if the target product was successfully synthesised. This synthesis and purification is outlined in detail in the experimental section. The synthesis was repeated twice by the same method and no target product was seen in the crude products of the two subsequent attempts at the synthesis. The crude products were purified by column chromatography but no target product was seen. The main details for the other methods used in the attempted synthesis of compound **380** are given in table 17. Attempts one to four give the conditions tried for the one pot method. Attempts five to eighteen give the conditions tried for the attempts at the synthesis of compound **380** using the *bis*-alcohol precursor **368** as the starting material. Using this method 0.5 mmol of **368** was dissolved in the designated solvent, under nitrogen, and followed by addition of the base. The reaction mixture was brought to the designated temperature and terephthaloyl dichloride was added. The reaction was stirred at the designated temperature for the allotted time and then quenched by addition of water and worked up as done in the one pot method. All volumes of solvent are normalised for 1.00 mmol of morphine as starting material.

Attempt	Starting material	Base (eq.)	Solvent (vol.)	Temp.	Time (h)
1	Morphine. **335**	5.0 eq. NEt_3	125 mL DCM	RT	4
2	Morphine **335**	5.0 eq. NEt_3	125 mL DCM	RT	72
3	Morphine **335**	5.0 eq. NEt_3	125 mL DCM	40 ^oC	48
4	Morphine **335**	6.4 eq. NEt_3	125 mL DCM	40 ^oC	48
5	**368**	5.0 eq. NEt_3	32 mL DCM	RT	48
6	**368**	1.1 eq. DMAP	200 mL DCM	RT	48
7	**368**	5.0 eq. NEt_3	200 mL DCM	RT	48
8	**368**	108 eq. NEt_3	15 mL DCM	-78 ^oC for 4 hours, then RT	24
9	**368**	64 eq. NEt_3	260 mL DCM	-78 ^oC for 4 hours, then RT	24
10	**368**	12 eq. NEt_3	250 mL DCM	40 ^oC	72
11	**368**	1.1 eq. DMAP	125 mL DCM	RT	72
12	**368**	13 eq.K_2CO_3	170 mL DCM	RT	72
13	**368**	6 eq. K_2CO_3	125 mL DCM	RT	24
14	**368**	6 eq. Na_2CO_3	250 mL DCM	40 ^oC	24
15	**368**	6 eq. Na_2CO_3	250 mL chloroform	70 ^oC	24
16	**368**	5.0 eq. NEt_3	125 mL chloroform	70 ^oC	24
17	**368**	7.2 eq. NEt_3	300 mL DCM	40 ^oC	72
18	**368**	7.2 eq. NEt_3	300 mL DCM	RT	72

Table 17: Conditions used in the attempted synthesis of compound **380**.

After each attempted synthesis attempts were made at the isolations of the target product, by column chromatography, recrystallisations (from single solvent and solvent mixes), solid-liquid extraction, liquid-liquid extraction and some attempts by short-path vacuum distillation on a Buchi glass oven B-585 Kugelrohr. The target product,

macrocycle **380**, was not seen in the products (crude or purified) of any of these reactions. The following set of NMR spectra are a typical example of the results from the column chromatography of one of the synthesis attempts, each NMR represents a fraction obtained from the column.

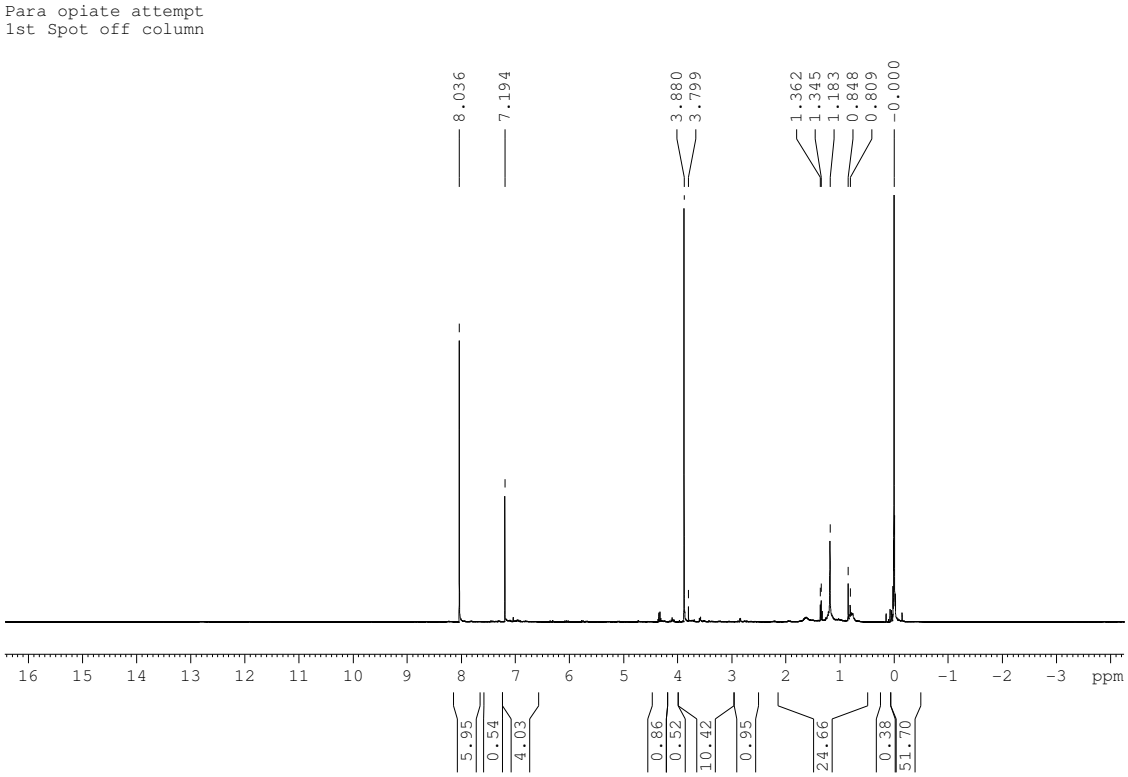


Figure 86: NMR of 1st fraction.

In the first fraction there is clearly no opiate material and hence clearly no target product. The diacid of the diacid chloride starting material, terephthalic acid, is seen at 8.036 ppm.

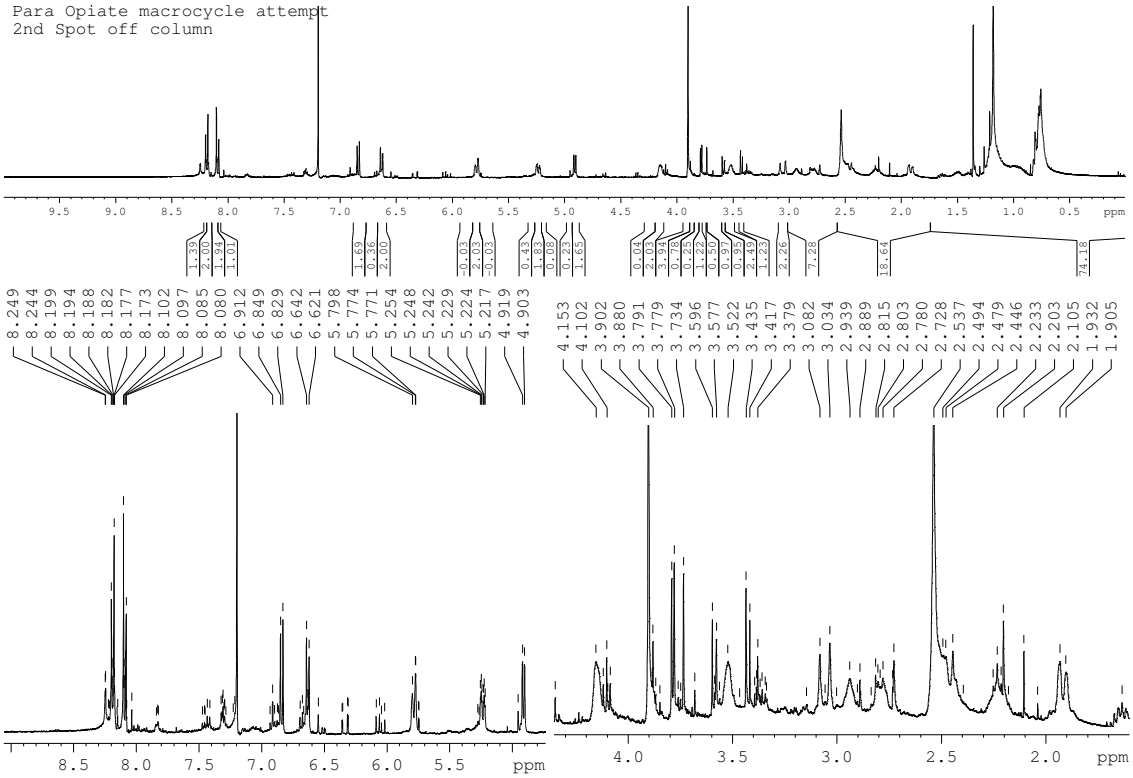


Figure 87: NMR of 2nd fraction.

In the second fraction there is opiate present but it appears to be 3-*O*-morphinyl terephthalate, the single adduct of morphine and terephthaloyl dichloride. There are two aromatic peaks in the region of 8.0 to 8.3, but these peaks are not singlets as expected for the target product but instead are doublets with bias towards each other signifying that they couple each other. This would suggest it is from the terephthaloyl moiety with one side as the acid and the other as the ester.

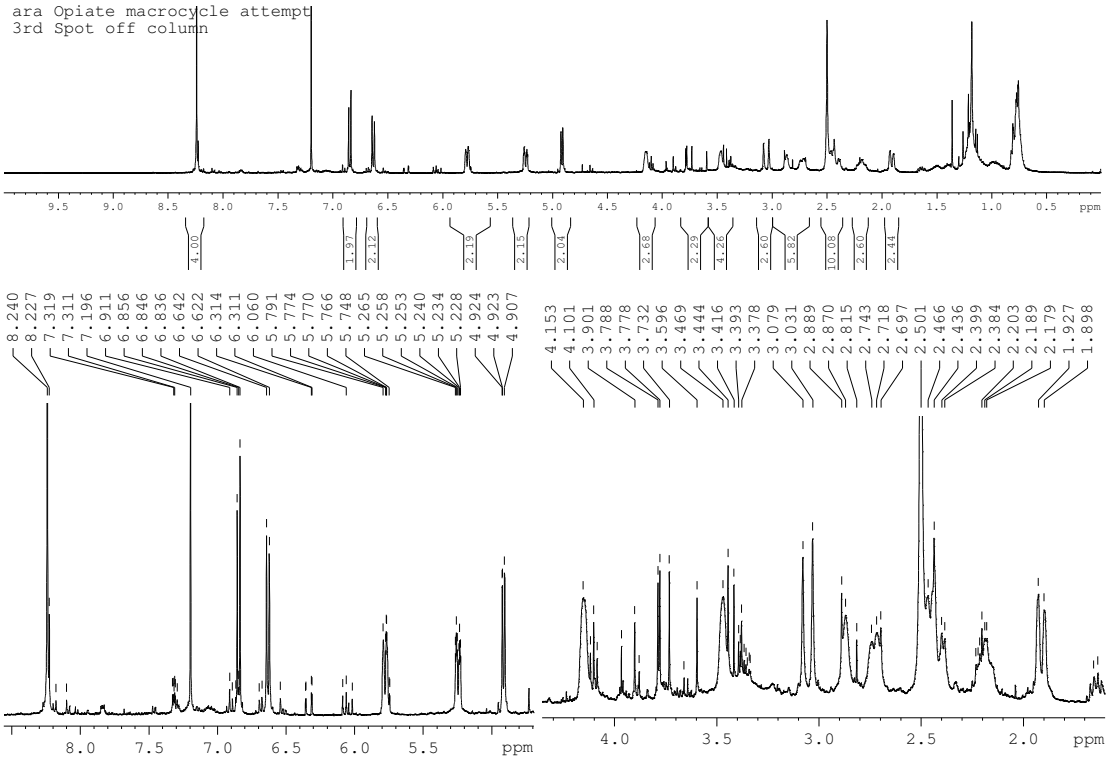


Figure 88: NMR of 3rd fraction.

The third fraction contains opiate product but it appears to be *bis*(3-morphinyl) terephthalate, compound **368**. There is one singlet at 8.24 and this integrates correctly to the opiate peaks thus suggesting that this is compound **368.**

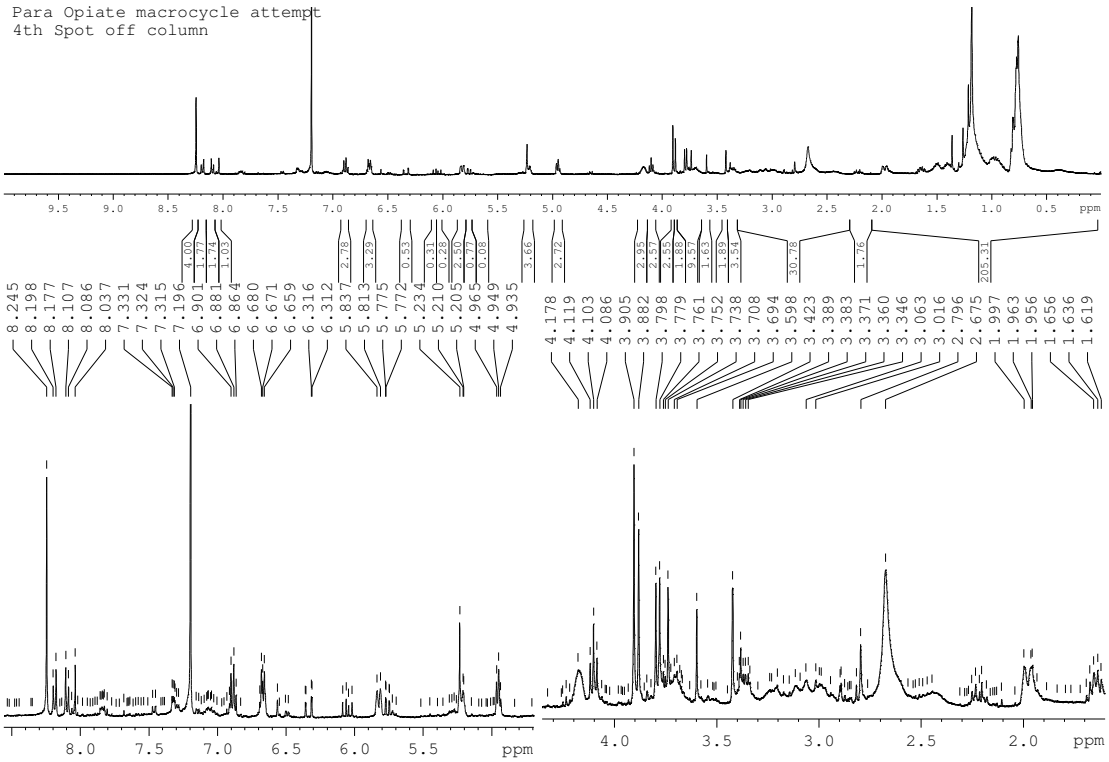


Figure 89: NMR of 4th fraction .

The fourth fraction contains opiate product but it appears to be impure. It appears as mixture of *bis*(3-morphinyl) terephthalate and *O*-morphinyl terephthalate. Although this is a postulated mixture, we are confident that the isolated material is not the target product nor is it pure.

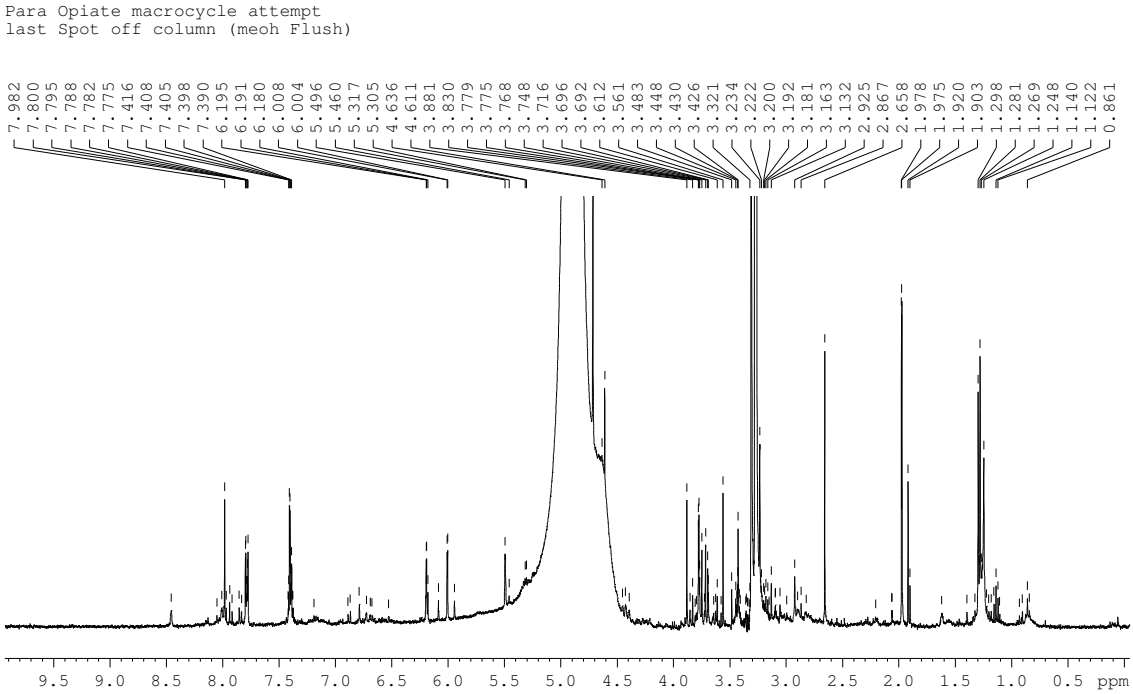


Figure 90: NMR of Last fraction (methanol flush)

When all the fractions seen by TLC had eluted, the column was flushed with methanol. After removal of the solvent *in vacuo* this fraction gave the NMR spectrum shown in figure 90 above. Again this fraction seems impure, although again the exact product is unsure it can be clearly seen that the target product is not present.

After the synthesis of compound **385** was tried, unsuccessfully, by the nineteen methods it was decided to prepare some macrocycles using the aliphatic diacid chlorides. The diacid dichlorides, diglycolyl dichloride and dimethylmalonyl chloride, were next to be attempted. They are more flexible and it was thought that one of the problems for the synthesis of compound **385** may have been that each of the units being brought together were inflexible and therefore this could hinder the cyclisation reaction. Attempts were then made to synthesise compounds **386** and **387**. Synthesis and isolation of each of these were attempted three times, all of which were from morphine carried out from the morphine starting material (rather than from the *bis*-morphine open structures) using the one pot general method. Table 18 shows the details of the solvent, base, temperature and time used in the attempted synthesis of

compounds **386** and **387**. As with table 17 all volumes used are normalised for 1.00 mmol of morphine starting material.

Product, Attempt	Base (type and equivalents)	Solvent (type and volume)	Temperature	Time (h)
386, A	5.0 equivalents NEt_3	125 mL DCM	RT	4
386, B	5.0 equivalents NEt_3	125 mL DCM	RT	72
386, C	10 equivalents NEt_3	125 mL DCM	40 ^oC	48
387, A	5.0 equivalents NEt_3	125 mL DCM	40 ^oC	48
387, B	7.2 equivalents NEt_3	125 mL DCM	RT	48
387, C	5.0 equivalents NEt_3	20 mL DCM	40 ^oC	48

Table 18: Details of attempted synthesis of **386** *and* **387**.

After each synthesis attempts were made to purify the crude product and to isolate the target products. The target product was not isolated from these reactions, but the starting material (morphine) was recovered, typically in 70 % mass recovery.

The next macrocycles to be attempted were compounds **388-395**. The structures are shown in figure 83.

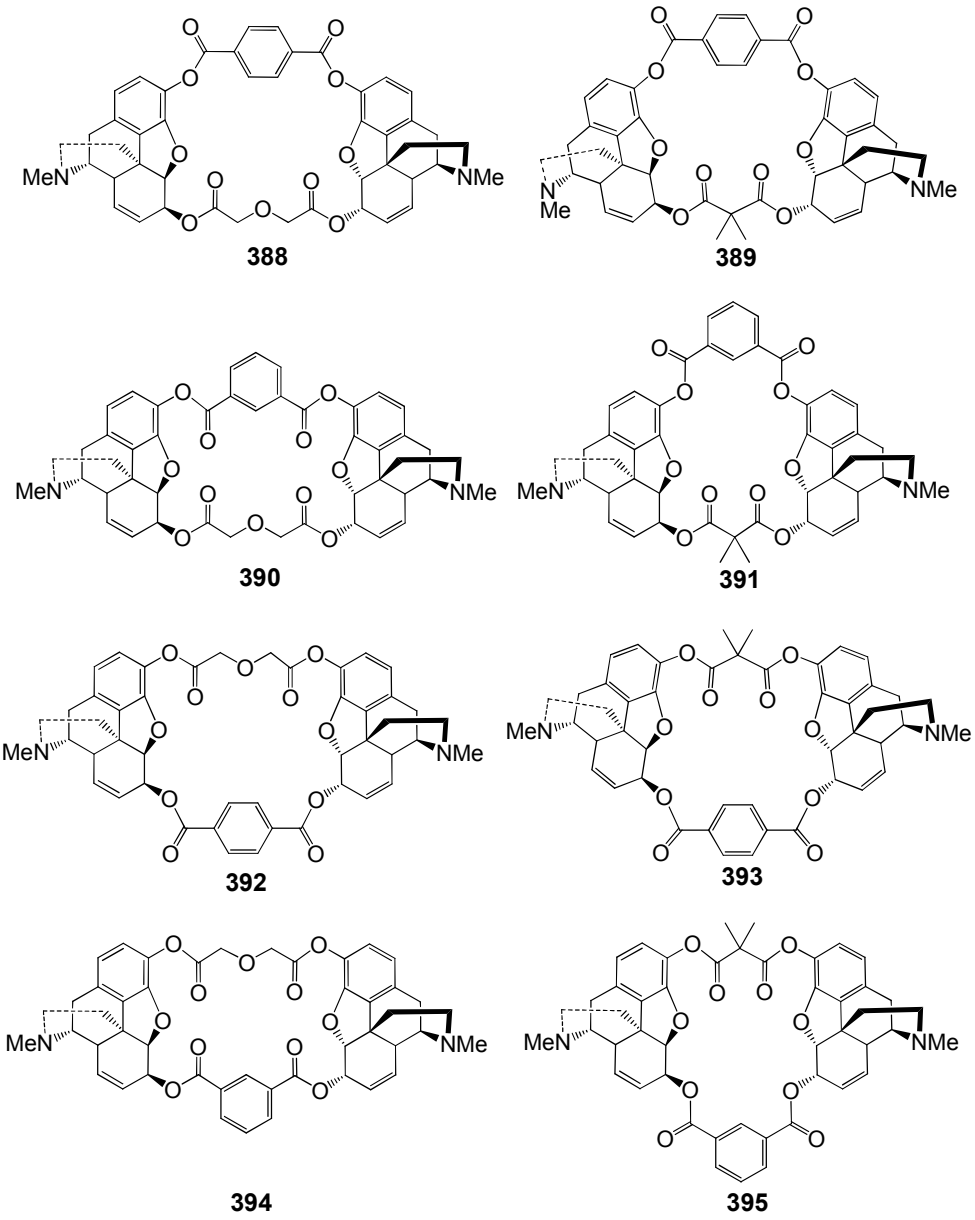


Figure 83: **388**-**395***, macrocycles with aromatic and aliphatic linkers combined which were not successfully isolated*

A mix of aliphatic and aromatic diacid chlorides were used in the attempted synthesis of these compounds. Each synthesis was attempted only once and each was carried out by the same method. This was the same method first used for the synthesis of **380** except the second step was left refluxing for seventy two hours. Again there were attempts made at the isolation of each product and again each attempt failed. In each case the crude product contained a mixture of unreacted morphine, typically 40-50 % mass recovery of the starting material, the left over diacid and also some phenol linked *bis*-morphine open structures, although these were not typically purified.

After each of the attempted synthesis above failed it was decided to try to synthesise compounds **375**-**379** and **381**-**385,** the analogues of each of the compounds which were synthesised in chapter two that have not already been attempted. These attempts were made in the final stages of the project in an effort to isolate a macrocycle containing morphine. Each of the synthesis attempts at these macrocycles were carried out using the one pot method and also from the phenol linked *bis*-morphine open structures, where they were available. The method for the one pot synthesis was the same as the general method from chapter two: the morphine was dissolved in dichloromethane with triethylamine under nitrogen at -15 ^{o}C and then half an equivalent of diacid dichloride was added. This was stirred at -15 ^{o}C then at room temperature for another hour. Another aliquot of triethylamine and dichloromethane were added. Another half equivalent of diacid dichloride was then dissolved in dichloromethane and added dropwise to the reaction. After the allotted time this was quenched with water, washed and the organic removed *in vacuo*. The synthesis of each of these products was attempted from the appropriate phenol linked *bis*-morphine structure. For this method the *bis*-morphine structure was dissolved in dichloromethane and triethylamine was added. Then the diacid dichloride was dissolved in dichloromethane and added dropwise to the reaction and left to stir overnight. The reaction was then quenched by addition of water and washed and evaporated to dryness. After each of these reactions, attempts were made to isolate the target products, however unsuccessfully.

The crude products from all of the attempts to produce macrocycles **375**-**387** were purified by column chromatography and in each case no target product was successfully isolated pure. In each case the results were similar to those reported for attempts 1-18 of the synthesis of **380** above. The first fraction was the diacid formed from the reaction of the acid chloride and water on quenching of the reaction. Each of the other fractions contained opiate compounds but no detectable target product.

Below in figures 91-99 are shown the NMR spectra of the fractions from the column chromatography of the crude product from the attempted synthesis of **378** and **383** as typical examples of the results obtained from each of the attempted synthesis of the macrocycles. Figures 91-95 are the spectra of the fractions isolated of the crude product obtained from the attempted synthesis of **378**.

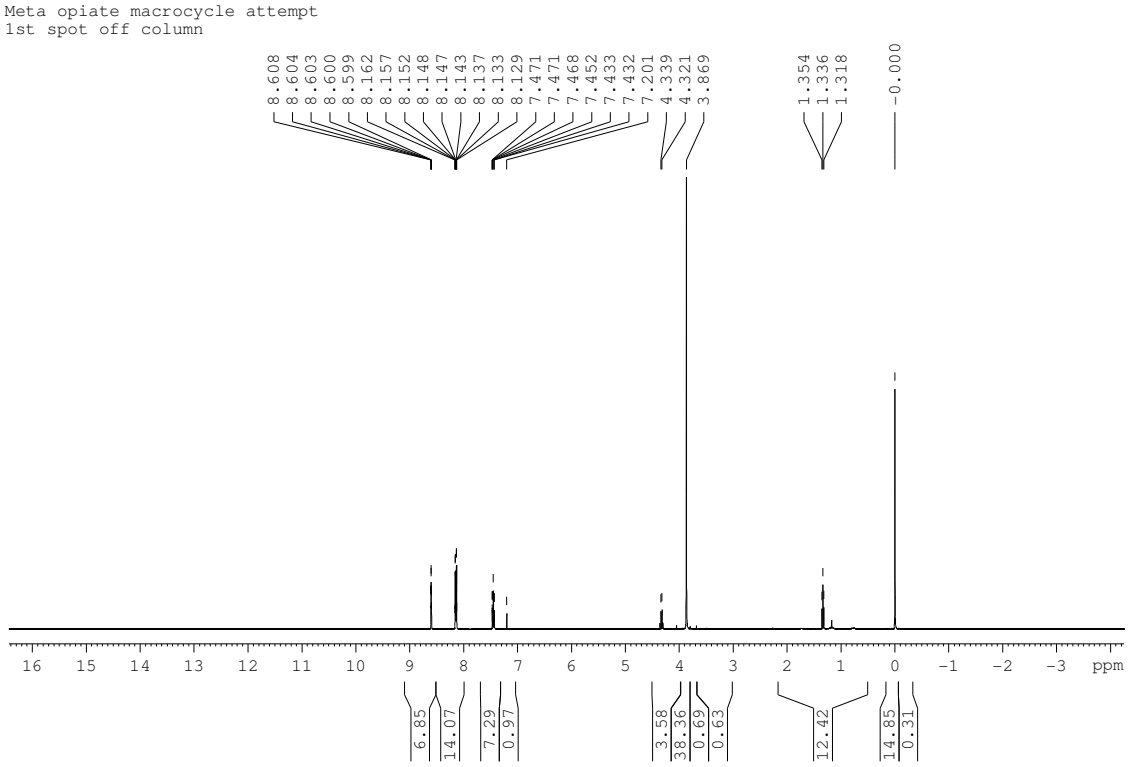


Figure 91: NMR of 1st fraction from the attempted synthesis of **378**

The ^{1}H-NMR spectrum of the 1st fraction shows there is clearly no opiate material and hence clearly no target product. The diacid of the diacid chloride starting material, isophthalic acid, is seen at 7.4, 8.1 and 8.6 ppm.

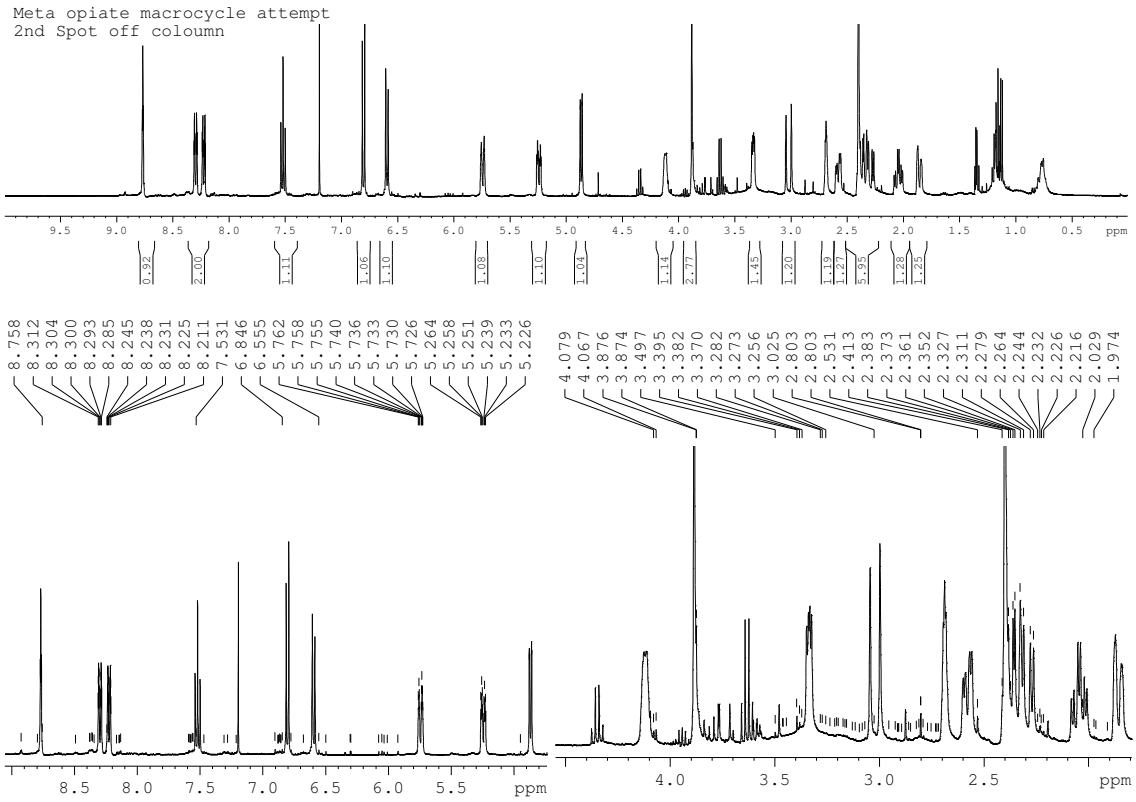


Figure 92: NMR of 2nd fraction from the attempted synthesis of **378**

In the ^{1}H-NMR spectrum of the 2nd fraction there is opiate product but it appears to be 3-*O*-morphinyl isophthalate, the single adduct of morphine and isophthaloyl dichloride.

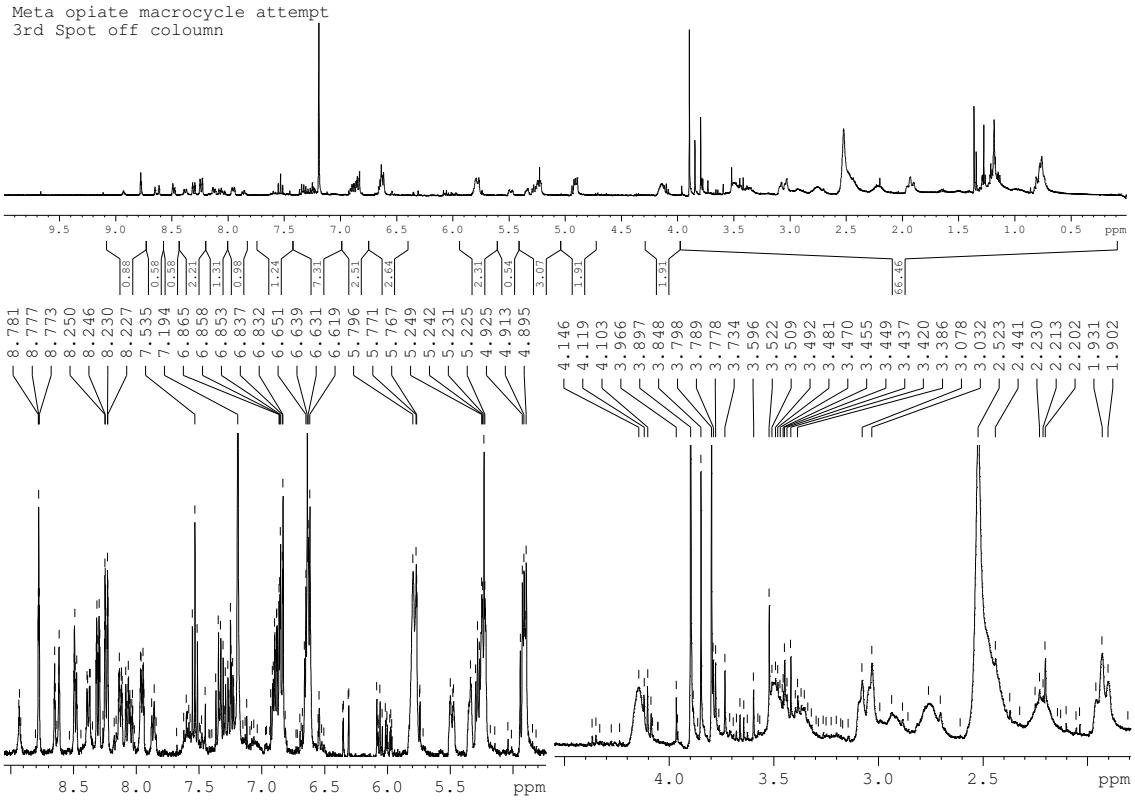


Figure 93: NMR of 3rd fraction from the attempted synthesis of **378**

In the ^{1}H-NMR spectrum of the third fraction (figure 93) there appears to be a mix of products, but most notably there is no sign of the target product (**378**).

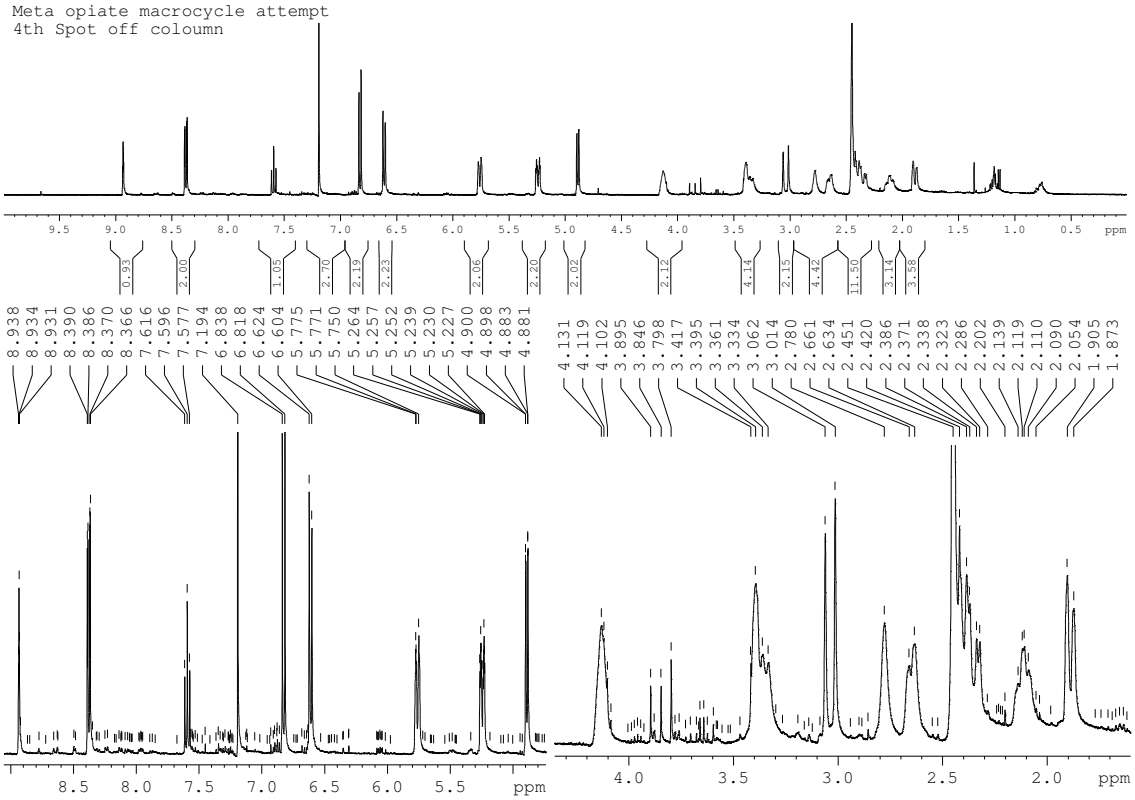


Figure 94: NMR of 4th fraction from the attempted synthesis of **378**

In the 4th fraction there is one pure isolated material, it is clearly *bis*(3-morphinyl) isophthalate (**369**) as seen in ^{1}H-NMR spectrum in figure 94 above.

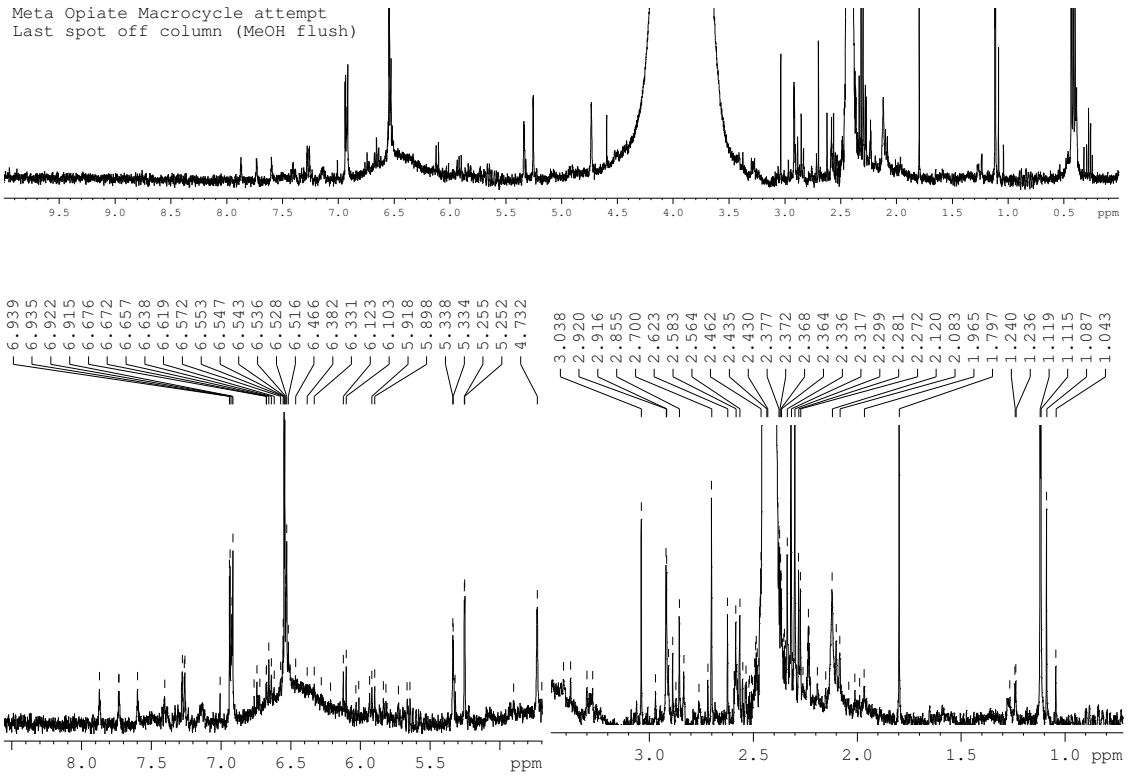


Figure 95: NMR of last fraction (methanol flush) from the attempted synthesis of **378**

Again this fraction seems impure, as seen in the ^{1}H-NMR spectra (figure 95). Although the exact product is unsure it can be clearly seen that the target product is not in the present.

The next set of ^{1}H-NMR spectra (figures 96-99) are of the fractions isolated after passing the crude product obtained from the attempted synthesis of **383** down a silica column.

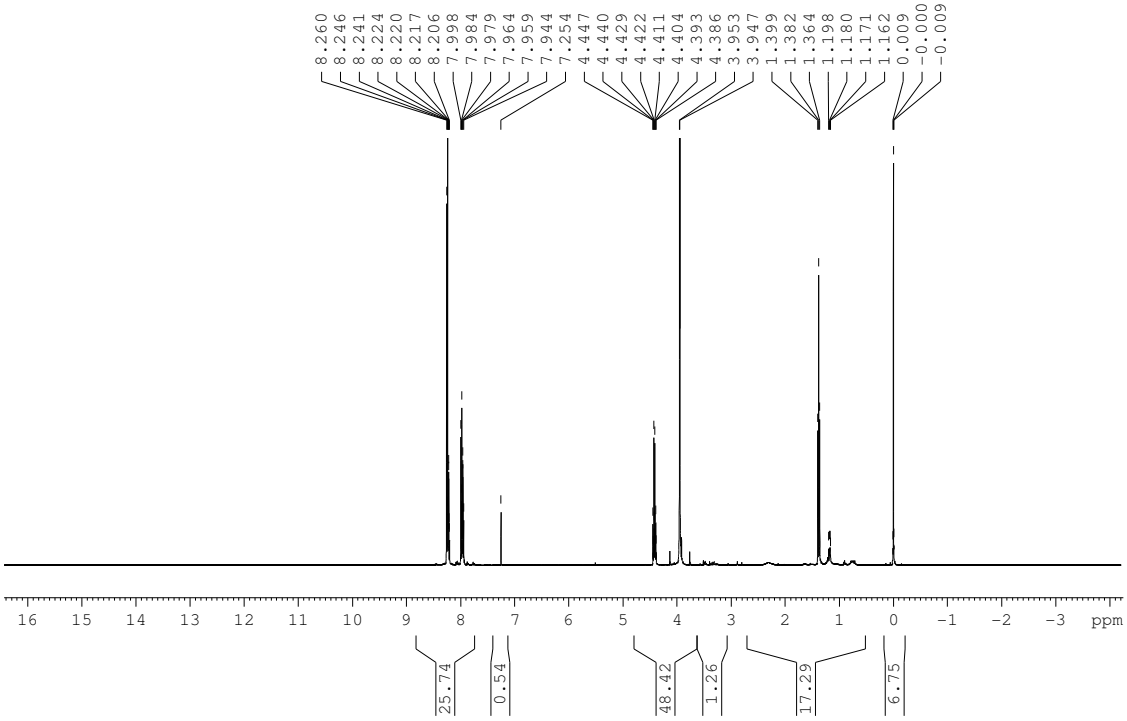


Figure 96: NMR of 1st fraction from the attempted synthesis of **383**

The ^{1}H-spectrum of the 1st fraction shows clearly that no opiate material is present in this fraction and hence clearly no target product. The diacid of the diacid chloride starting material, pyridine-2,6-dicarboxylic acid, is seen at 7.9 and 8.2 ppm.

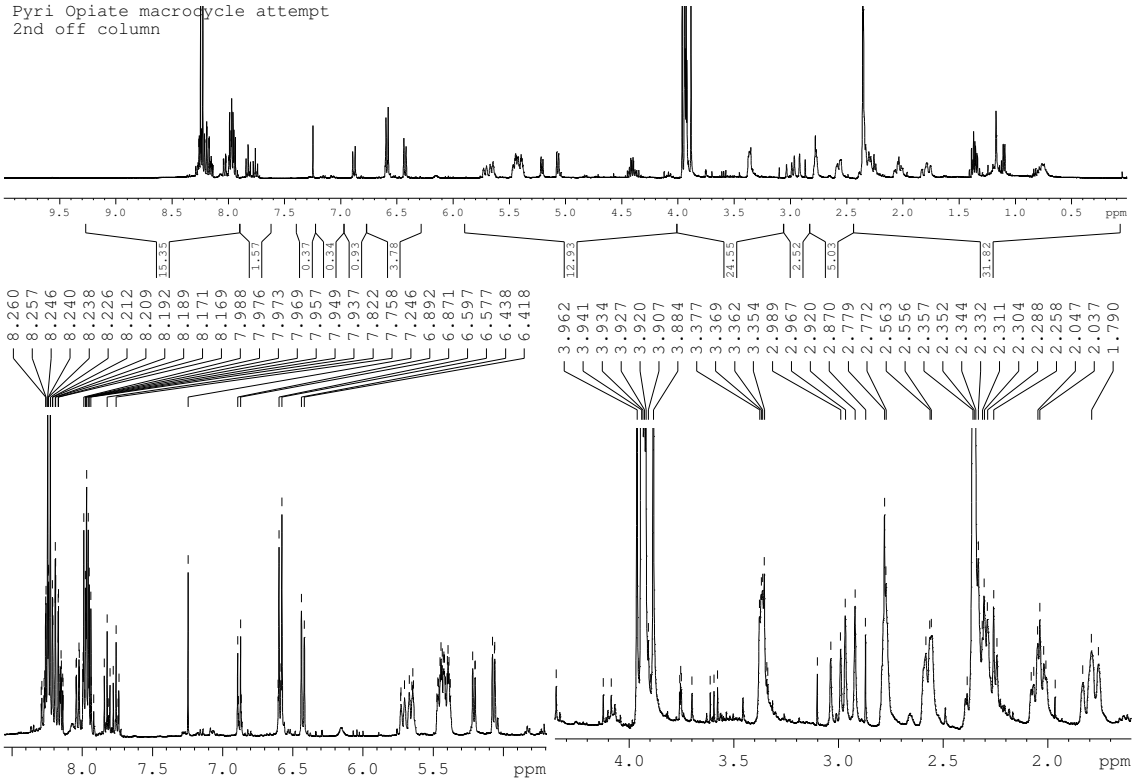


Figure 97: NMR of 2nd fraction from the attempted synthesis of **383**

In figure 97 there is no sign of the target product, although this fraction is impure, and there is a clear abundance of pyridine-2,6-dicarboxylic acid.

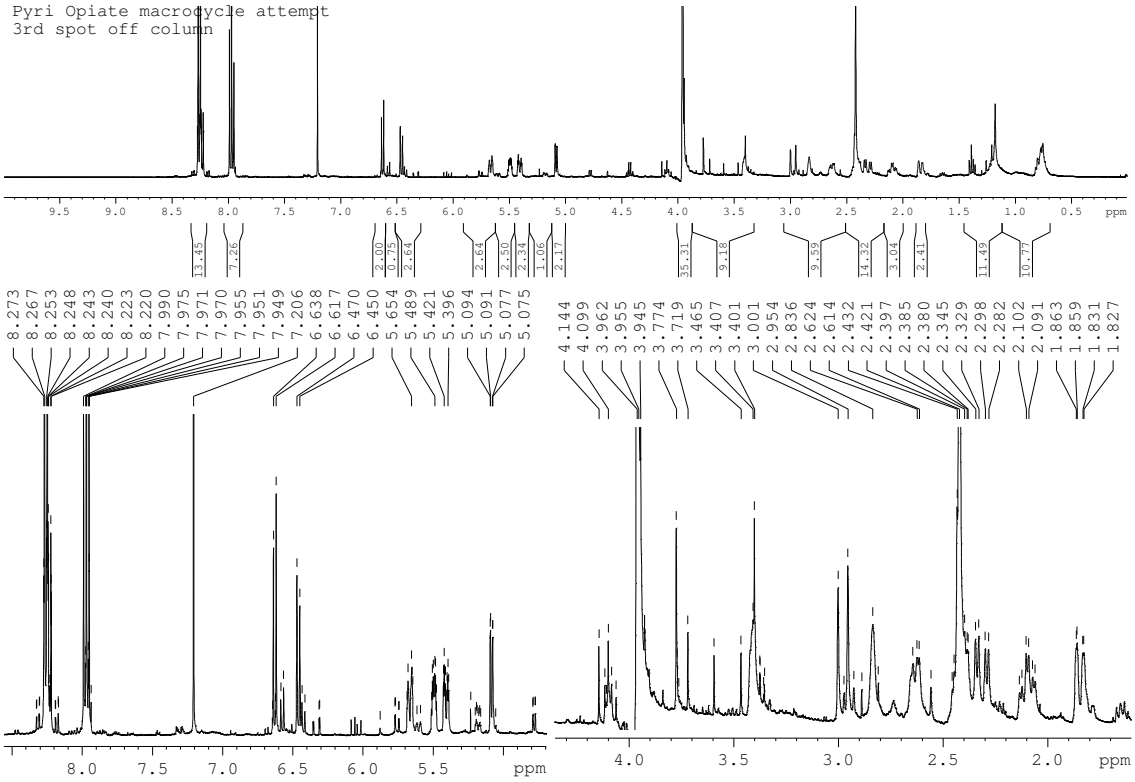


Figure 98: NMR of 3rd fraction from the attempted synthesis of **383**

In the third fraction it can be clearly seen again that there is no target product with there still being an abundance of the pyridine-2,6-dicarboxylic acid, alongside an impure opiate product.

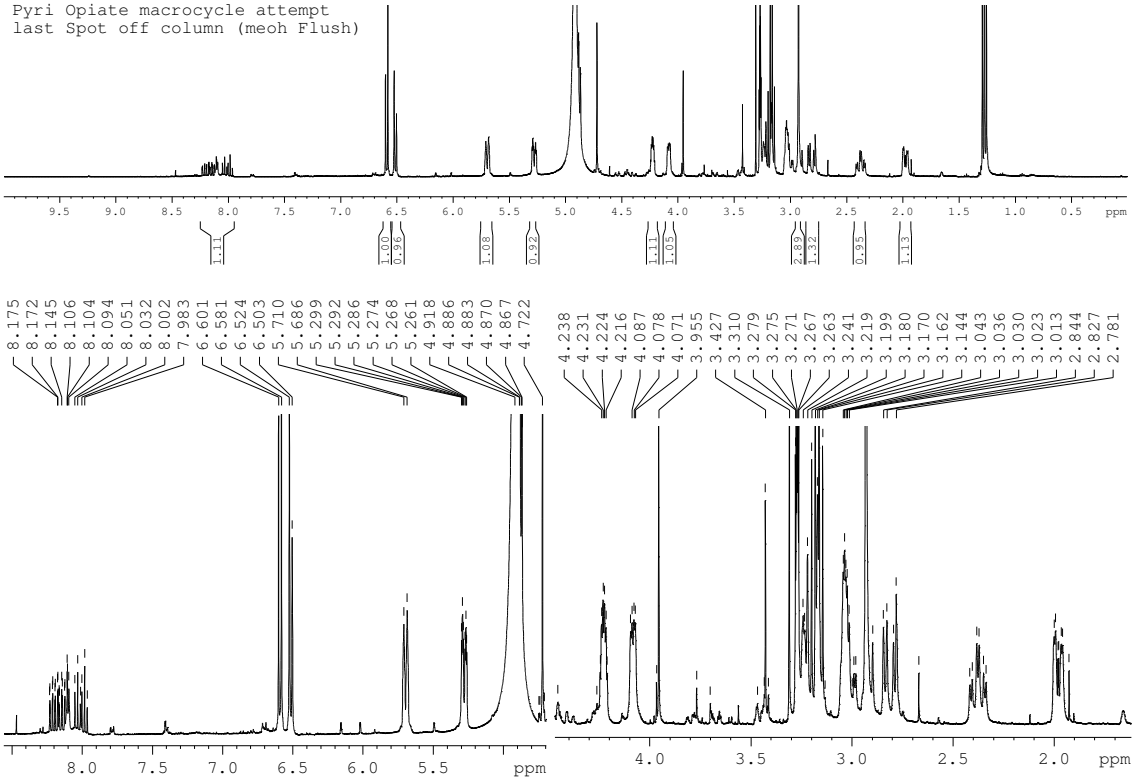


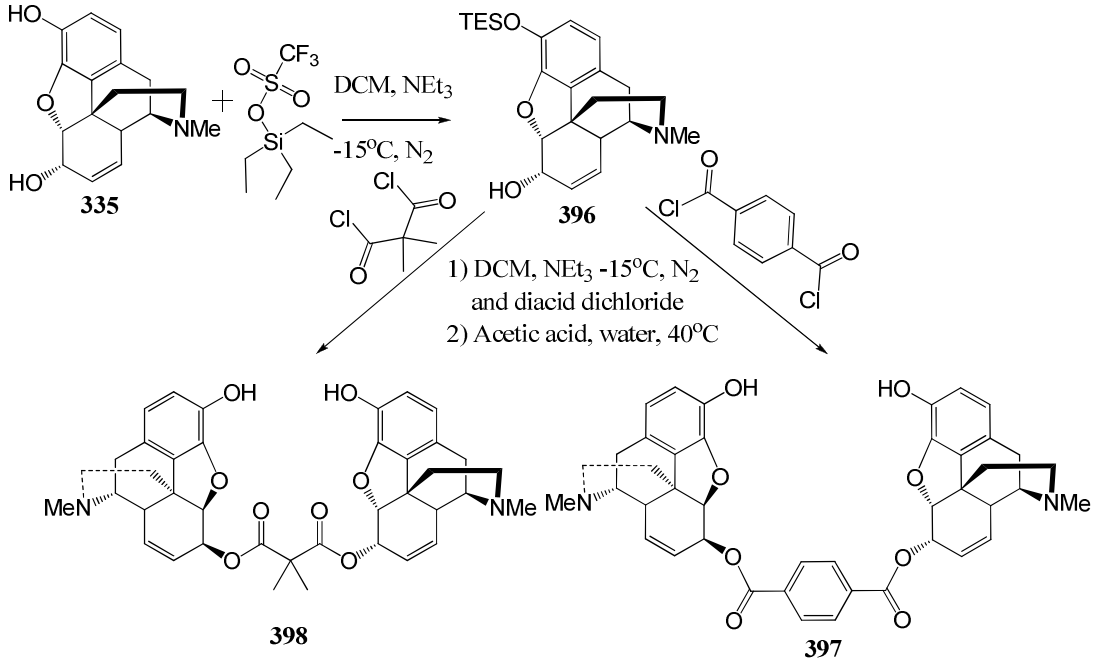
Figure 99: NMR of last fraction (methanol flush) from the attempted synthesis of **383**

The ^{1}H-NMR spectrum shown in figure 99 shows that the methanol flush is impure, although again the exact product is unsure it can be clearly seen that the target product is not present. Also there appears to be morphine starting material left over.

3.4: Attempts to synthesise the secondary alcohol linked morphine open structures.

After the attempted synthesis of the macrocycles detailed in section 3.3 proved fruitless it was decided to synthesise the 2^{o} alcohol linked *bis*-morphine open structures. Then to attempt the synthesis of the macrocycles from the 2^{o} alcohol linked morphine open structures. It was postulated that the increased reactivity of the phenols would lead to a higher conversion for the reactions with the diacid chloride on attempts to synthesise the macrocycles. Also preparing the more labile ester bonds last may lead to less decomposition products, as the ester bonds can be broken in the presence of base or acid and there is base used in the reaction. Hydrogen chloride is also a side product of the reaction and this could react with the ester to break the bond. If the more stable

bond is formed first then this is less likely to decompose under the reaction conditions and therefore it is more likely that the target product will be synthesised. The first step was the synthesis of TES protected morphine, **396,** and then using compound **396** as a starting material attempts were made at the synthesis of compounds **397** and **398**. Scheme 32 shows the synthetic pathway for the synthesis of compounds **396**, **397** and **398**.



Scheme 32: Failed Synthetic pathway for **397** *and* **398.**

The TES protected morphine (**396**) was successfully synthesised and isolated. Using **396** attempts were made at the synthesis and isolation of compounds **397** and **398**. The same reaction conditions were used for both compounds. The first attempt was using the same method for the synthesis of the phenol linked morphine open structures. The reactions were also carried out using dimethylaminopyridine instead of triethylamine. No reaction occurred with dimethylaminopyridine and only the starting material, compound **396**, was recovered from the reactions. From the reaction using triethylamine the TES protected intermediates were synthesised, although not isolated pure. Multiple attempts at the purification failed and instead it was decided to proceed to the deprotection step and to isolate pure after deprotection. This decision was made with the experiences of the synthesis of the analogous 2-(2-hydroxyethoxy)phenol compounds (**346** and **347**). With **346** and **347** if the protected intermediate was not pure it was easier to isolate the final product than it was to isolate the intermediate. For this reason the impure intermediate compounds were deprotected. The deprotection

was to be carried out in the same way as done previously, in 4:1 acetic acid: water at 40 ^{o}C monitored every 10 minutes by thin layer chromatography. The target product decomposed during the deprotection within 20 minutes. This may have happened for a number of reasons including: the products may be more soluble in the acid solution than the analogous 2-(2-hydroxyethoxy)phenol compounds were; and the ester bond of the target product may be more sensitive to acidic hydrolysis than that of the analogous 2-(2-hydroxyethoxy)phenol compounds. This could happen because the pK_a of the hydroxy group on 3-*O*-triethylsilyl morphine is calculated to be 13.5 ±0.2 compared to that of the hydroxy group in 2-{2-[(triethylsilyl)oxy]phenoxy}ethanol calculated to be 14.3 ±0.1. The pKa's were calculated using Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris (© 1994-2009 ACD/Labs). Work is ongoing within the research group to attempt the isolation compounds **397** and **398** and other related analogues, and then, if successfully isolated, to use these as starting materials in attempts to make the macrocycles discussed in this chapter.

Conclusion:

In conclusion five new open structures containing morphine, **368**-**372**, were successfully synthesised and isolated.

Although there were attempts at the synthesis and isolation of twenty one new macrocycles none of the macrocycles were isolated. The synthesis of compound **380** was attempted nineteen times, starting with the optimised method developed for **353**. Although this product was not isolated pure it seems to have been synthesised by the first attempt, but this can only be confirmed by ^{1}H and ^{13}C NMR at this stage.

The other macrocycles attempted (**375**-**379** and **381**-**395**) were not isolated and it is unsure if these macrocycles were successfully synthesised and not isolated or if the synthesis was unsuccessful.

The macrocycles discussed in this chapter were the primary synthetic target at the beginning of the research, but as with all research the focus changes. This impacted on the volume of work done in an effort to synthesise and isolate these macrocycles. For this project the focus changed from the isolation of these macrocycles to the optimisation of the synthesis of *bis*(2-(2-hydroxyphenoxy)ethyl) 2,2-dimethylmalonate and other work related to the possible biological activity of this compound. The

optimisation part of this work was already discussed in chapter two and the biological activity and the work related to the will be discussed in chapter five.

The synthesis of these macrocycles is still seen as an important goal of the research this project has started. For this reason the synthesis and isolation of the triethylsilyl protected morphine (**396**) and the attempted isolation of the secondary alcohol linked open structures (**397** and **398**) was carried out. With some further work it is intended to synthesise and isolate these open structures, with less acid being used or maybe a lower temperature. Then if successfully isolated compounds **397** and **398** could be used in the synthesis of the macrocycles.

Another method for the synthesis and isolation of **380** may be to return to the optimisation of **353**. As the method from reaction AD (tables 2 and 3, pages 67) was the only method used in the attempted synthesis of compound **380** which appeared to yield the target product it is likely that a new method with higher yield of **353** would give compound **380** in sufficient yield that it could be isolated.

A factor that may be hindering the synthesis of the morphine macrocycles is the rigid structure of morphine in comparison to the 2-(2-hydroxyethoxy)phenol used to develop the synthesis. This rigidity decreases the chances of the linear open structures, e.g. *bis*(3-morphinyl) phthalate, **370**, flexing into a position in which the macrocyclisation can occur. To overcome this there are two options, one is to obtain a more rigid diol and to use this for the method development and the other is to do the method development using morphine. The use of a more rigid diol in place of the 2-(2-hydroxyethoxy)phenol comes with the risk of the developed method being non-transferable to the morphine. The first step in this second method utilised to overcome the rigidity was to switch the order of linking and closing the macrocycles. The synthesis was attempted by first linking across the aliphatic alcohols and then closing the macrocycles between the phenols. By carrying out the synthesis by this method the cyclisation step of the models more closely matches that of the morphine so the same method could work to close the opiate macrocycle as was used to close the model. Also if the reaction between the acid chloride and the alcohol is more likely to occur then each time the alcohol and acid chloride come close enough to react then they are more likely to react. Thus, although there is less chance of them coming close, because of the rigid structure, each time they are close they are more likely to react to form the target product. This method of synthesis was shown to have worked with the model

systems but compounds **397** and **398** were not successfully isolated to test the method for the synthesis of the envisaged opiate macrocycles.

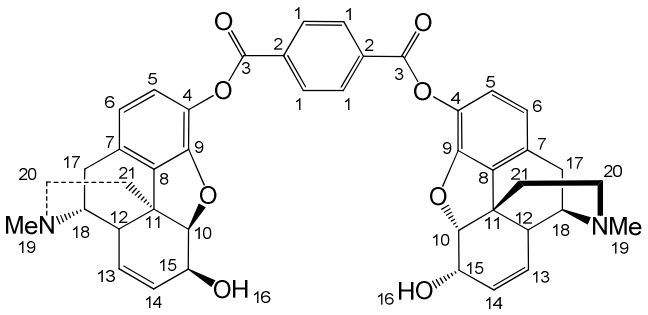
Although it is envisaged that future work preparing models may aide the development of the opiate macrocycles but will most likely be due to observed trends rather than direct method transfer. Carrying out the method development using morphine as the starting material may be expensive, due to the cost of morphine, its storage, disposal and licensing, but the method development should be done using morphine in future.

Experimental:

All chemicals were purchased from Sigma/Aldrich and used as received, with the exception of the morphine hydrochloride trihydrate which was purchased from Johnson Matthey Macfarlan Smith, Edinburgh, and dried for one week under vacuum before being used. When necessary solvents were purified prior to use and stored under nitrogen. Dichloromethane was distilled from CaH_2 and triethylamine was distilled and stored over potassium hydroxide pellets. Commercial grade reagents were used without further purification. Davisil 60A silica gel was used for thin layer and column flash chromatography. Melting points were determined using a Stuart melting point, SMP3, apparatus and are uncorrected. Infrared spectra were recorded on an IR is Perkin Elmer FT-IR system, spectrum GX spectrometer. Optical rotations were measure on a Perkin Elmer 343 Polarimeter in HPLC grade chloroform. Liquid chromatography time-of-flight mass spectrometry was recorded on a Waters Corp. Liquid Chromatography-Time of flight mass spectrometer from Micromass MS Technologies Centre. NMR spectra were obtained on a Bruker AC 400 NMR spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. The ^{1}H and ^{13}C NMR chemical shifts (ppm) are relative to tetramethylsilane. All coupling constants (*J*) are in Hertz.

Synthesis of the phenol linked open structures:

Synthesis of *bis*(3-morphinyl) terephthalate, compound 368:



Morphine hydrochloride (0.339 g, 1.06 mmol) was dissolved in dry dichloromethane (10.0 mL) at room temperature under nitrogen and then chilled to -15 ^{o}C. Dry triethylamine (0.5 mL, 3.6 mmol) was added while stirring and maintaining the temperature at -15 ^{o}C. Terephthaloyl dichloride (107 mg, 0.53 mmol) was dissolved in dry dichloromethane (10.0 mL) and added to the reaction mixture. The reaction mixture was stirred for 1 hour, allowed to warm to room temperature and stirred for another hour. The reaction was quenched by adding distilled water (10.0 mL), and stirring for twenty minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (10.0 mL X10), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Drying *in vacuo* for 1 week yielded the pure product (85 %, 0.316 g, 0.45 mmol) as a colourless powder.

^{1}H NMR ($CDCl_3$): δ(ppm) 8.22 (4H, s, *H1*), 6.81 (2H, d, *J* = 8.0 *Hz*, *H5*), 6.60 (2H, d, *J* = 8.0 *Hz*, *H6*), 5.73 (2H, dt *J* = 9.6*, 3.0 Hz*, *H13*), 5.25 (2H, dt, *J* = 9.6*,* 2.8 *Hz*, *H14*), 4.88 (2H, d, *J* = 2.8 *Hz*, *H10*), 4.12 (2H, Broad s, *H15*), 3.42 (2H, Broad s, *H16*), 3.31 (2H, dd, *J* = 6.0, 3.0 *Hz*, *H17*), 3.01 (2H, d, *J* = 19.0 *Hz*, *H20*), 2.64 (2H, t, *J* = 3.0 *Hz*, *H18*), 2.54 (2H, dd, *J* = 12.2*,* 3.0 *Hz*, *H12*), 2.36 (6H, s, *H19*), 2.29 (4H, td, *J* = 19.0*,* 5.9 *Hz*, *H's 17 and 20*), 2.01 (2H, td, *J* = 12.0*,* 5.9 *Hz*, *H21*), 1.85 (2H, d(broad), *J* = 12.0 *Hz*, *H21*).

^{13}C NMR ($CDCl_3$): δ(ppm) 163.22 (*C3*), 148.73 (*C9*), 134.20 (*C2*), 133.39 (*C4*), 133.29 (*C14*), 132.56 (*C8*), 131.68 (*C7*), 130.50 (*C1*), 127.87 (*C13*), 121.07 (*C6*), 120.09 (*C5*), 92.53 (*C15*), 65.86 (*C18*), 58.87 (*C10*), 46.39 (*C20*), 43.13 (*C19*), 42.69 (*C11*), 40.45 (*C12*), 35.24 (*C21*), 20.77 (*C17*).

IR (KBr disc): σ(cm^{-1}) 3511, 3031, 2911, 2847, 2801, 2362, 2345, 1735, 1617, 1560, 1491, 1451, 1375, 1350, 1243, 1199, 1173, 1155, 1118, 1099, 1072, 1034, 1015.

MP: 165-167 ^{o}C

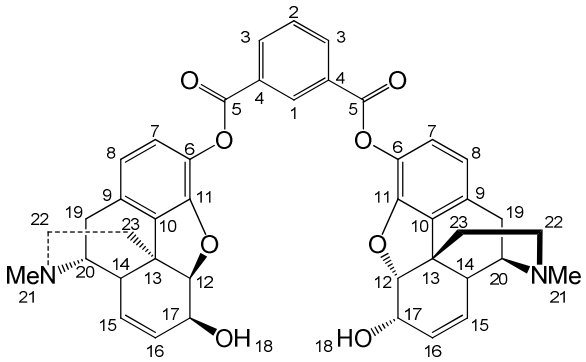
Optical Rotation (0.3 c, $CHCl_3$, 589nm, 20 ^oC): -152 ^{o}

Calculated exact mass for product: ($C_{42}H_{40}N_2O_8$) 700.2785

Calculated exact mass for product: ($C_{42}H_{40}N_2O_8H^+$) 701.2857

Found, HRMS (EI, 70 eV): 701.2890

Synthesis of *bis*(3-morphinyl) isophthalate, compound 369:



Morphine hydrochloride (0.339 g, 1.06 mmol) was dissolved in dry dichloromethane (10.0 mL) at room temperature under nitrogen and chilled to -15 ^oC. Dry triethylamine (0.5 mL, 3.6 mmol) was added while stirring and maintaining the temperature at -15 ^oC. Isophthaloyl dichloride (107 mg, 0.53 mmol) was dissolved in dry dichloromethane (10.0 mL) and added to the reaction mixture. The reaction mixture was stirred for 1 hour, allowed to warm to room temperature and was stirred for another hour. The reaction was quenched by adding distilled water (10.0 mL), and stirring for twenty minutes and then transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was then washed with distilled water (10.0 mL X10) and dried over $MgSO_4$ and the solvent was removed *in vacuo*. Drying *in vacuo* for 1 week yielded the pure product (63 %, 0.213 g, .033 mmol) as a colourless powder.

^1H NMR ($CDCl_3$): δ(ppm) 8.93 (1H, t, *J* = 1.6 *Hz, H1*), 8.38 (2H, dd, *J* = 7.5, 1.6 *Hz, H3*), 7.59 (1H, t, *J* = 7.5 *Hz, H2*), 6.83 (2H, d, *J* = 8.0 *Hz, H7*), 6.61 (2H, d, *J* = 8.0 *Hz, H8*), 5.76 (2H, d, *J* = 10.0 *Hz, H15*), 5.25 (2H, dt, *J* = 10.0*,* 2.4 *Hz, H16*), 4.88 (2H, d, *J* = 3.6 *Hz, H12*), 4.13 (2H, q, *J* = 2.0 *Hz*, *H17*), 3.43 (2H, q, *J* = 3.6 *Hz, H19*), 3.04 (2H, d, *J* = 17.2 *Hz, H22*), 2.79 (2H, t, Broad s*, H20*), 2.68 (2H, dd, *J* = 17.0*,* 4.3 *Hz, H14*), 2.46 (6H, s, *H21*), 2.43-2.34 (4H, m, *H's 19* and *22*), 2.12 (2H, td, *J* = 11.7*,* 4.3 *Hz, H23*), 1.89 (2H, d(broad), *J* = 11.7 *Hz, H23*).

^{13}C NMR ($CDCl_3$): δ(ppm) 163.20 (*C5*), 148.73 (*C11*), 135.39 (*C3*), 134.24 (*C16*), 133.18 (*C6*), 132.50 (*C1*), 132.21 (*C10*), 131.71 (*C4*), 129.67 (*C2*), 129.13 (*C9*),

127.84 (*C*15), 121.12 (*C8*), 1120.08 (*C7*), 92.50 (*C12*), 65.87 (*C20*), 58.90 (*17*), 46.40 (*C22*), 43.12 (*C21*), 42.69 (*C13*), 40.46 (*C14*), 35.24 (*C23*), 20.78 (*C19*).

IR (KBr disc): σ(cm^{-1}) 3504, 2927, 2361, 2341, 1868, 1847, 1830, 1772, 1734, 1700 1684, 1653, 1616, 1559, 1540, 1490, 1473, 1456, 1397, 1300, 1197, 1065.

MP: 216-218 ^{o}C

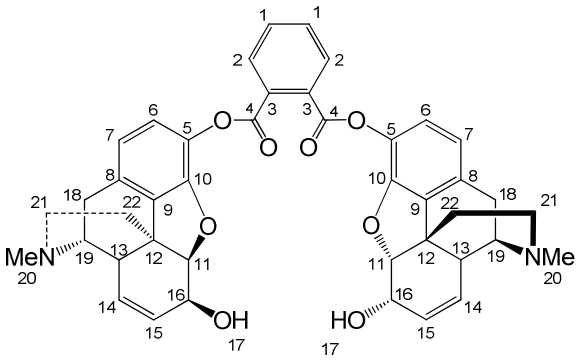
Optical Rotation (0.32 c, $CHCl_3$, 589 nm, 20 ^{o}C): -173.5 ^{o}

Calculated exact mass for product: ($C_{42}H_{40}N_2O_8$) 700.2785

Calculated exact mass for product: ($C_{42}H_{40}N_2O_8H^+$) 701.2857

Found, HRMS (EI, 70 eV): 701.2890

Synthesis of *bis*(3-morphinyl) phthalate, compound 370:



Morphine hydrochloride (0.339 g, 1.06 mmol) was dissolved in dry dichloromethane (10.0 mL) at room temperature under nitrogen and then chilled to -15 ^{o}C. Dry triethylamine (0.5 mL, 3.6 mmol) was added while stirring and maintaining the temperature at -15 ^{o}C. Phthaloyl dicarbonyl dichloride (0.147 mL, 0.53 mmol) was dissolved in dry dichloromethane (10.0 mL) and added to the reaction mixture. The reaction mixture was stirred for 1 hour, then allowed to warm to room temperature and was stirred for another hour. The reaction was quenched by adding distilled water (10.0 mL), and stirring for twenty minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (10.0 mL X10), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Recrystallisation from chloroform:hexane yielded the pure product (16 %, 0.060 g, 0.08 mmol) as a colourless powder.

^{1}H NMR ($CDCl_3$): δ(ppm) 7.89 (2H, dd, *J* = 5.7*,* 3.3 *Hz, H2*), 7.60 (2H, dd, *J* = 5.7*,* 3.3 *Hz, H1*), 6.81 (2H, d, *J* = 8.0 *Hz, H6*), 6.53 (2H, d, *J* = 8.0 *Hz, H7*), 5.67 (2H, dt *J* = 10.0*, 1.2 Hz, H14*), 5.20 (2H, dt, *J* = 8.6*,* 1.5 *Hz, H15*), 4.76 (2H, d, *J* = 3.*8 Hz, H11*), 4.07 (2H, Broad s*, H16*), 3.32 (2H, dd, *J* = 8.6, 3.8 *Hz, H18*), 3.00 (2H, d, *J* = 18.8 *Hz,*

H21), 2.65 (2H, Broad s, *H19*), 2.54 (2H, dd, *J* = 17.5, 4.3 *Hz, H13*), 2.39 (6H, s, *H20*), 2.32 (2H, dd, *J* = 12.3, 3.3 *Hz, H18*), 2.26 (2H, dd, *J* = 17.5, 1.2 *Hz, H21*), 1.98 (2H, td, *J* = 11.2, 4.3 *Hz, H22*), 1.71 (2H, d(broad), *J* = 11.2 *Hz, H22*).

^{13}C NMR ($CDCl_3$): δ(ppm) 163.78 (*C4*), 147.75 (*C10*), 133.27 (*C5*), 131.57 (*C1*), 131.08 (*C9*), 130.87 (*C's 3 and 15*), 130.15 (*C8*), 128.92 (*C14*), 126.53 (*C2*), 120.48 (*C7*), 118.69 (*C6*), 91.17 (*C11*), 64.97 (*C16*), 57.91 (*C19*), 45.37 (*C21*), 41.98 (*C20*), 41.54 (*C12*), 39.24 (*C13*), 34.04 (*C22*), 19.81 (*C18*).

IR (KBr disc): σ(cm^{-1}) 2926, 2361, 2341, 1868, 1772, 1734, 1717, 1700, 1684, 1653, 1617, 1559, 1540, 1507, 1490, 1457, 1419, 1261, 1050.

MP: 139-141 ^{o}C

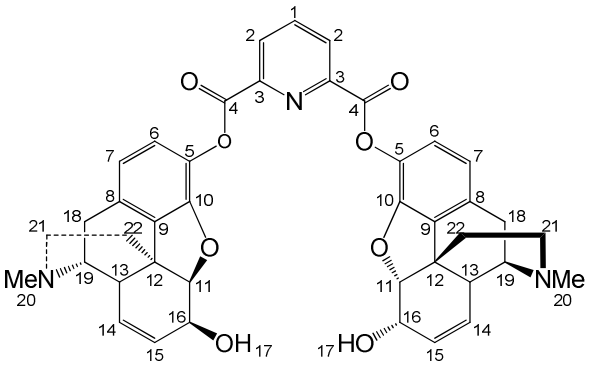
Optical Rotation (0.22 c, $CHCl_3$, 589 nm, 20 ^{o}C): -136 ^{o}

Calculated exact mass for product: ($C_{42}H_{40}N_2O_8$) 700.2785

Calculated exact mass for product: ($C_{42}H_{40}N_2O_8H^+$) 701.2857

Found, HRMS (EI, 70 eV): 701.2890

Synthesis of *bis*(3-morphinyl) pyridine-2,6-dicarboxylate, compound 371:



Morphine hydrochloride (0.339 g, 1.06 mmol) was dissolved in dry dichloromethane (10.0 mL) at room temperature under nitrogen and then chilled to -15 ^{o}C. Dry potassium carbonate (0.9 g, 6.5 mmol) was added while stirring and maintaining the temperature at -15 ^{o}C. Pyridine dicarbonyl dichloride (103 mg, 0.53 mmol) was dissolved in dry dichloromethane (10.0 mL) and added to the reaction mixture. The reaction mixture was stirred for 1 hour, then allowed to warm to room temperature and was stirred for another hour. The reaction was quenched by adding distilled water (10.0 mL), and stirring for twenty minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (10.0 mL X10), then dried over $MgSO_4$ and the

solvent was removed *in vacuo*. This yielded the pure product (50 %, 0.178 g, 0.26 mmol) as a white solid without the need for further purification.

^{1}H NMR ($CDCl_3$): δ(ppm) 8.43 (2H, d, *J* = 7.8 *Hz, H2*), 8.04 (1H, t, *J* = 7.8 *Hz, H1*), 6.88 (2H, d, *J* = 8.0 *Hz, H6*), 6.59 (2H, d, *J* = 8.0 *Hz, H7*), 5.73 (2H, d, *J* = 9.7 *Hz, H14*), 5.24 (2H, d, *J* = 7.9 *Hz, H15*), 4.88 (2H, d, *J* = 3.4 *Hz, H11*), 4.12 (2H, Broad s, *H17*), 3.35 (2H, dd, *J* = 7.9, 3.4 *Hz, H18*), 3.04 (2H, d, *J* = 18.8 *Hz, H21*), 2.70 (2H, Broad s, *H19*), 2.54 (2H, dd, *J* = 15.3, 1.9 *Hz, H13*), 2.41 (6H, s, *H20*), 2.35 (2H, dd, *J* = 12.6, 3.5 *Hz, H18*), 2.27 (2H, dd, *J* = 15.3, 5.8 *Hz, H21*), 2.06 (2H, td, *J* = 12.2, 5.8 *Hz, H22*), 1.84 (2H, d(broad), *J* = 12.2 *Hz, H22*).

^{13}C NMR ($CDCl_3$): δ(ppm) 162.16 (*C4*), 148.73 (*C10*), 147.61 (*C3*), 138.57 (*C1*), 134.24 (*C5*), 132.32 (*C15*), 131.89 (*C's 8 and 9*), 129.44 (*C14*), 127.62 (*C2*), 121.36 (*C7*), 119.99 (*C6*), 92.49 (*C11*), 66.03 (*C19*), 58.96 (*C16*), 53.47 (*C21*), 46.41 (*C20*), 42.99 (*C12*), 42.68 (*C13*), 35.10 (*C22*), 20.91 (*C18*).

IR (KBr disc): σ(cm^{-1}): 3525, 2927, 2361, 2341, 1869, 1844, 1772, 1734, 1700, 1684, 1653, 1617, 1559, 1540, 1507, 1490, 1456, 1419, 1396, 1318, 1243, 1200, 1121.

MP: 218-220 ^{o}C

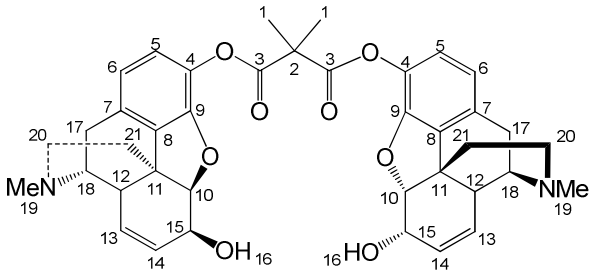
Optical Rotation (0.20 c, $CHCl_3$, 589 nm, 20 ^{o}C): -170 ^{o}

Calculated exact mass for product: ($C_{41}H_{39}N_3O_8$701.2737

Calculated exact mass for product: ($C_{41}H_{39}N_3O_8H^+$) 702.2810

Found, HRMS (EI, 70 eV): 702.2826

Synthesis of *bis*(3-morphinyl) 2,2-dimethylmalonate, compound 372:



Morphine hydrochloride (0.339 g, 1.06 mmol) was dissolved in dry dichloromethane (10.0 mL) at room temperature under nitrogen and then chilled to -15 ^{o}C. Dry triethylamine (0.5 mL, 3.6 mmol) was added while stirring and maintaining the temperature at -15 ^{o}C. Dimethylmalonyl chloride (0.112 mL, 0.53 mmol) was dissolved in dry dichloromethane (10.0 mL) and added to the reaction mixture. The reaction mixture was stirred for 1 hour, then allowed to warm to room temperature and

was stirred for another hour. The reaction was quenched by adding distilled water (10.0 mL) and stirring for twenty minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (10.0 mL X10), then dried over $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatography with 15 % methanol and 1 % aqueous ammonium hydroxide in dichloromethane yielded the pure product (4.2 %, 16 mg, 0.02mmol) as a colourless powder.

^{1}H NMR ($CDCl_3$): δ(ppm) 6.75 (2H, d, *J* = 8.0 *Hz, H5*), 6.57 (2H, d, *J* = 8.0 *Hz, H6*), 5.71 (2H, d, *J* = 10.0 *Hz, H13*), 5.20 (2H, d, *J* = 10.0 *Hz, H14*), 4.86 (2H, d, *J* = 6.7 *Hz, H10*), 4.10 (2H, Broad s*, H15*), 3.51 (2H, d, *J* = 16.1 *Hz, H17*), 3.42 (2H, Broad s*, H16*), 3.01 (2H, d, *J* = 16.1 *Hz, H20*), 2.81 (2H, Broad s*, H18*), 2.67 (2H, Broad s*, H*12), 2.47 (6H, s, *H*19), 2.48-2.34 (4H, m, *H's 17 and 20*), 2.15 (2H, Broad s, *H21*), 1.87 (2H, d(broad), *J* = 12.2 *Hz, H21*), 1.64 (6H, s, *H1*).

^{13}C NMR ($CDCl_3$): δ(ppm) 171.80 (*C3*), 147.82 (*C9*), 133.24 (*C4*), 131.68 (*C14*), 131.24 (*C7*), 130.80 (*C8*), 126.40 (*C13*), 120.03 (*C5*), 118.96 (*C6*), 91.22 (*C10*), 65.75 (*C18*), 57.90 (*C15*), 51.75 (*C2*), 45.534 (*C20*), 41.82 (*C19*), 41.49 (*C11*), 39.01 (*C12*), 33.82 (*C21*), 21.85 (*C1*), 19.91 (*C17*).

IR (KBr disc) σ(cm^{-1}): 3534, 3450, 2992, 2927, 2878, 2361, 1876, 1843, 1754, 1607, 1536, 1507, 1459, 1425, 1399, 1312, 1291, 1250, 1211, 1183, 1154, 1098.

MP: 143-145 ^{o}C

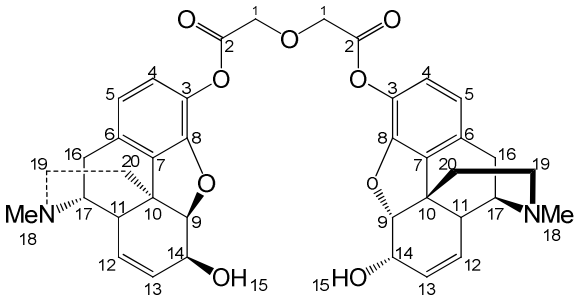
Optical Rotation (0.3 c, $CHCl_3$, 589 nm, 20 ^{o}C): -77 ^{o}

Calculated exact mass for product: ($C_{39}H_{42}N_2O_8$) 666.2941

Calculated exact mass for product: ($C_{39}H_{42}N_2O_8H^+$) 667.3014

Found: HRMS (EI, 70 eV) 667.3029

Attempted Synthesis of *bis*(3-morphinyl) diglycolate, compound 373:



Morphine hydrochloride (0.339 g, 1.06 mmol) was dissolved in dry dichloromethane (10.0 mL) at room temperature under nitrogen and then chilled to -15 ^{o}C. Dry triethylamine (0.5 mL, 3.6 mmol) was added while stirring and maintaining the temperature at -15 ^{o}C. Diglycolyl chloride (0.085 mg, 0.495 mmol) was dissolved in dry dichloromethane (10.0 mL) and added to the reaction mixture. The reaction mixture was stirred for 1 hour, then allowed to warm to room temperature and was stirred for another hour. The reaction was quenched by adding distilled water (10.0 mL), and stirring for twenty minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (10.0 mL X10), then dried over $MgSO_4$ and the solvent was removed *in vacuo*.

The mass recovery of the product was 432 %, 1.431 g, and the crude product was soluble in the aqueous, not the organic as expected, because of this the crude product had almost all the impurities mixed in with it and hence gave a very high crude yield.

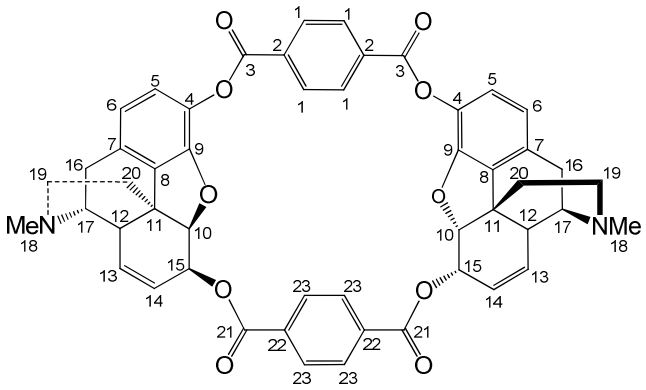
The product was not isolated pure; there are inorganic impurities present which are not visible by NMR. But this means the optical rotation, MP and IR spectrum could not be recorded.

^{1}H NMR ($CDCl_3$): δ(ppm) 6.62 (2H, d, *J* = 8.1 *Hz, H4*), 6.56 (2H, d, *J* = 8.1 *Hz, H5*), 5.61 (2H, d, *J* = 10.0 *Hz, H12*), 5.24 (2H, dd, *J* = 10.0 *Hz,* 0.7 *Hz, H13*), 5.13 (2H, d, *J* = 7.*5 Hz, H9*), 4.19 (4H, s*, H1*), 4.07 (2H, broad d, *J* = 7.5 *Hz, H14*), 3.2-1.5 (22H, m*, H's 11 and 16 to 22*).

^{13}C NMR ($CDCl_3$): δ(ppm) 176.99 (*C2*), 144.48 (*C8*), 138.29 (*C3*), 128.83 (*C13*), 128.50 (*C7*), 126.46 (*C6*), 122.76 (*C12*), 120.73 (*C4*), 117.87 (*C5*), 85.96 (*C9*), 69.69 (*C17*), 67.48 (*C14*), 67.25 (*C1*), 60.77 (*C19*), 47.74 (*C18*), 40.80 (*C10*), 40.34 (*C11*), 38.01 (*C20*), 32.07 (*C16*).

Calculated exact mass for product: ($C_{38}H_{40}N_2O_9$) 668.2734

Attempted synthesis of cyclo[3'-(6'-morphinyl terephthalate)(3-morphinyl)terephthalate], macrocycle 380



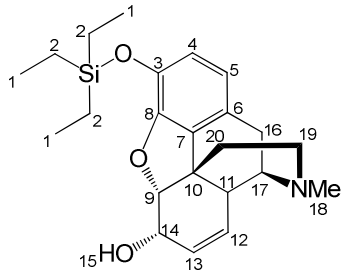
Morphine hydrochloride (0.325 g, 1.01 mmol) was dissolved in dry DCM (10.0 mL) at room temperature under nitrogen and then chilled to -15 ^{o}C. Dry triethylamine (0.35 mL, 2.5 mmol) was added. Terephthaloyl dichloride (102 mg, 0.506 mmol) was dissolved in dry DCM (5.0 mL) and added to the reaction mixture. The reaction mixture was stirred for one hour, then allowed to warm to room temperature and was stirred for one hour. DCM (60.0 mL) and triethylamine (0.35 mL, 2.5 mmol) were added. The reaction solution was heated to reflux. Terephthaloyl dichloride (102 mg, 0.506 mmol) was dissolved in dry DCM (50.0 mL) and added dropwise to the reaction flask. This reaction mixture was stirred for four hours at reflux. The reaction was quenched by adding distilled water (20.0 mL), cooling to room temperature and stirring for twenty minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (20 mL X10), then dried over $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatography using 10 % methanol in dichloromethane followed by two consecutive recrystallisations from chloroform:hexane resulted in the product (5.48 %, 0.023 g) which was not pure. MS, IR, MP and optical rotation were not recorded at this point as it was intended to carry out this analysis once the title compound had been isolated pure. By NMR the product appeared to be present, as presented in figures 83 and 85. The NMR data given below was from this impure product. Further recrystallisations from the same solvent mix did not improve the purity of this product. Further attempts of recrystallisations from other solvents and solvent mixes proved fruitless. The product was then washed with dilute hydrochloric acid (5.0 mL, 0.1 M) with the aim to form the hydrochloride salt of the product which would dissolve in the water and could then be extracted pure with the addition of a

mild base. The NMR data for each of the products from this did not contain the target product, this was either due to decomposition of the product by the alkali and alkaline conditions it was exposed to or because the product was not successfully synthesised. As such the MS, IR, MP and optical rotation could not be recorded. Repeat synthesis of this product failed to isolate the title compound.

^{1}H NMR ($CDCl_3$): δ(ppm) 8.06 (4H, s, *H1*), 7.73 (4H, s, *H23*), 7.08 (2H, d, *J* = 7.9 *Hz*, *H6*), 6.64 (2H, d, *J* = 7.9 *Hz*, *H5*), 5.78 (2H, dt, *J* = 9.3*,* 2.5 *Hz*, *H13*), 5.49 (2H, dt, *J* = 9.3*,* 1.9 *Hz*, *H14*), 5.37 (2H, d, *J* = 7.0 *Hz*, *H10*), 5.24 (2H, dd, *J* = 7.0*,* 1.9 *Hz*, *H15*), 3.2-1.5 (22H, m, *H's 12 and 16-20*).

^{13}C NMR ($CDCl_3$): δ(ppm) 163.77 (*C21*), 162.52 (*C3*), 147.82 (*C9*), 132.63 (*C2*), 132.46 (*C4*), 131.65 (*C8*), 130.23(*C22*), 128.81 (*C1*), 128.77 (*C23*), 128.01 (*C13*), 127.42 (*C7*), 120.85 (*C6*), 119.12 (*C14*), 118.61 (*C5*), 87.15 (*C10*), 68.09 (*C15*), 45.71 (*C17*), 41.81 (*C19*), 41.35 (*C18*), 38.97 (*C11*), 33.71 (*C12*), 28.68 (*C20*), 19.73 (*C16*).

Synthesis of 3-*O*-triethylsilyl morphine, compound 396:



Morphine hydrochloride (6.620 g, 20.572 mmol) was dissolved in dry dichloromethane (62.0 mL) under nitrogen at room temperature. Triethylamine (3.0 mL) was added. TES triflate (4.65 mL, 20.572 mmol) was added to the reaction mixture. This was stirred overnight at room temperature. The reaction was quenched by the addition of water (20.0 mL) and stirring for 20 minutes. The reaction mixture was filtered and the liquid transferred to a separation funnel and was then washed with distilled water (30.0 mL X6). The organic layer was then dried over $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatography with 20 % methanol in dichloromethane was carried out on the product isolated from the organic layer to yield pure target product (45 %, 3.70 g, 9.26 mmol) as a pale yellow liquid. Morphine (50 %, 2.935 g, 10.29 mmol) was also recovered as unreacted starting materials. This indicates a 95 % recovery of the starting material.

As this product was an intermediate its infrared spectrum was not recorded.

^{1}H NMR ($CDCl_3$): δ(ppm) 6.50 (1H, d, *J* = 8.0 *Hz, H4*), 6.40 (1H, d, *J* = 8.0 *Hz, H5*), 5.58 (1H, d quintet, *J* = 9.9, 2.6 *Hz, H12*), 5.20 (1H, dt, *J* = 9.9, 3.1 *Hz, H13*), 4.77 (1H, d, *J* = 1.2 *Hz, H9*), 4.09 (1H, dt, *J* = 2.6, 1.2 *Hz, H14*), 3.29 (1H, q, *J* = 3.1 *Hz, H16*), 2.94 (1H, d, *J* = *18.4 Hz, H19*), 2.60 (1H, t, *J* = 3.1 *Hz, H17*), 2.53 (1H, dd, *J* = 12.2, 5.1 *Hz, H11*), 3.36 (3H, s, H18), 2.37-2.31 (1H, m, *H19*), 2.23 (1H, dd, *J* = 18.4, 3.1 *Hz, H16*), 2.00 (1H, td, *J* = 11.6, 5.1 *Hz, H20*), 1.77 (1H, broad d, *J* = 11.6 *Hz, H20*), 0.91 (9H, t, *J* = 7.9 *Hz, H1*), 0.66 (6H, q, *J* = 7.9 *Hz, H2*).

^{13}C NMR (CDCl3): δ(ppm) 147.32 (*C8*), 136.14 (*C3*), 132.33 (*C13*), 130.12 (*C7*), 127.21 (*C12*), 126.50 (*C6*) 119.76 (*C5*), 118.56 (*C4*), 89.93 (*C9*), 65.42 (*C14*), 57.84 (*C17*), 45.41 (*C19*), 41.95 (*C18*), 41.87 (*C10*), 39.52 (*C11*), 32.25 (*C20*), 19.57 (*C16*), 5.57 (*C1*), 3.96 (*C2*).

Calculated exact mass for product: ($C_{23}H_{33}NO_3Si$) 399.2230

Calculated exact mass for product: ($C_{23}H_{33}NO_3SiH^+$) 400.2302

Found: HRMS (EI, 70 eV) 400.2319

Bibliography:

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Chapter 4

Metal Picrate Extraction studies with the Synthesised Compounds and Metal Templatation reactions

4.1 Introduction:

This chapter outlines the metal picrate extraction studies carried out on selected products synthesized in this project. The aim of this chapter is to establish a general view of the binding affinity of the macrocycles and their precursors, to a variety of metal cations, indicating which metal cation would bind to the corresponding macrocyclic compound. The picrate method is commonly used to determine extracting efficiencies of macrocyclic ethers and their precursors by measuring the relative distribution of a coloured alkali metal salt (in this case picrate) between water and an immiscible organic solvent in the presence of the crown ether.[73] If the polyether host is a powerful complexing agent, most of the colour will remain in the organic phase, whereas a colourless organic phase after extraction, indicates a low binding affinity.

Attempts to confirm the positive binding results have been made by attempting to force the macrocycle to bind to the metal 100 %, by repeating the extraction but using a large excess of the metal picrate in the hope of driving the binding to completion. The results from this will also determine the stability of the compounds to the extraction procedure, as it will be clear in the NMR spectra if the compounds degrade.

The relationship between the diameter of an alkali cation and the crown ether has been noted in earlier literature of crown ethers and this is best referred by Pedersen as the "hole-size-rule".[74] The cation diameters of the metals used in this study are shown in Table 19.[74,75]

Group I		Group II		Group III		Group IV	
Metal	Diameter (Å)	Metal	Diameter (Å)	Metal	Diameter (Å)	Metal	Diameter (Å)
Li^+	1.36	Mg^{2+}	1.44	La^{3+}	2.30	Pb(II)	2.40
Na^+	1.94	Ca^{2+}	1.98				
K^+	2.66	Zn^{2+}	1.48				
Cs^+	3.34	Sr^{2+}	2.26				
		Cd^{2+}	1.94				
		Ba^{2+}	2.68				
		Co(II)	1.68				
		Cu(II)	1.74				

Table 19: Metal Cation diameters

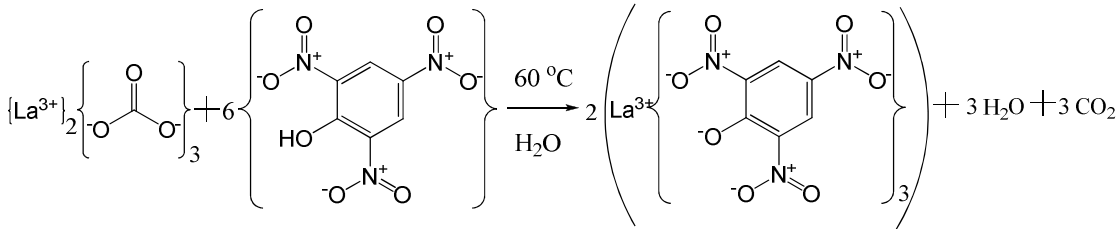
The results from the binding studies have then been used in macrocyclisation reactions using the templatation effect in an attempt to improve the yields of macrocycles obtained.

The results obtained in this investigation will be of use to potential applications of sensors, co-catalysts and metal complexation. Although this study did not examine these possibilities the work carried out in this chapter will aide the research group in the future.

4.2 Results and Discussion:

4.2.1: Metal Picrate Extraction Tests

Each of the products successfully isolated as part of this thesis were tested for their ability to extract a number of metal picrates. All the metal picrates (sodium, magnesium, calcium, zinc, potassium, lithium, barium, caesium, cadmium, cobalt, copper, strontium, lead and lanthanum) were synthesised by the same method, the example synthetic pathway of Lanthanum picrate is shown in scheme 33.



Scheme 33: Synthetic pathway of Lanthanum picrate

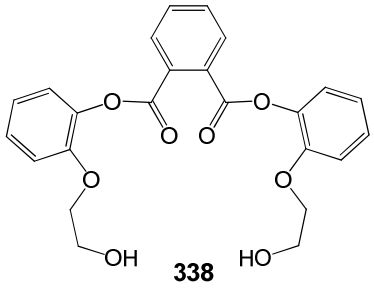
This method was agreed to by the head of safety in the department of chemical sciences prior to the synthesis being carried out. Under this agreement it was not permitted to fully dry the product due to their explosive nature. This meant yields could not be calculated. The method for the synthesis was straightforward. A saturated solution of picrate was made in DI water at 60 ^{o}C with gentle stirring. To this the relevant metal carbonate (as a dry powder) was slowly added to the stirring saturated picrate solution. As the carbonate was added gaseous carbon dioxide evolved. The carbonate was added slowly until the evolution of carbon dioxide ceased. The solution was then stirred for a further ten minutes to ensure the reaction had reached completion. The stirring bar was removed and the solution was chilled to 0 ^{o}C. The solution was then gravity filtered and the solid product collected. This synthesis was carried out with fourteen metal carbonates: Na_2CO_3; $MgCO_3$; $CaCO_3$; $ZnCO_3$; K_2CO_3; Li_2CO_3; $BaCO_3$; Cs_2CO_3; $CdCO_3$; $CoCO_3$; $CuCO_3$; $SrCO_3$; $PbCO_3$; and $La_2(CO_3)_3$.

Before the extractions were carried out a calibration curve was created for each metal picrate by making a series of solutions with concentrations over the range $7x10^{-5}$ M to $3.5x10^{-5}$ M by dilution from the $7x10^{-5}$ M stock solution of the picrate. Each of these solutions was made in triplicate and each had its absorbance measured. A calibration curve of concentration versus absorbance was drawn up; the coefficient of determination (r^2 value) for each calibration curve was $\geq$ 98 %. The calibration curves were used to calculate the concentrations of the extracted solutions. This error was seen in the blank extraction experiments and therefore results below 2 % extraction will be considered as 0 % extraction and will be reported as not successfully determined (ND).

The metal picrate extraction experiments were performed by using host solutions (macrocycle or a precursor) in chloroform and guest solutions (picrate) in DI water according to the procedure described by Pedersen. To do this a sample of each of the metal picrates was thoroughly dried *in vacuo* (90 ^{o}C, 48 h), a solution ($7x10^{-5}$ M) was made up and the extraction tests carried out. Each metal picrate was extracted with several of the products. Blank extractions were carried out for each of the picrate solutions, extracted with chloroform for comparison to the product solutions. When the blank extractions with barium, zinc and calcium picrates were carried out, it was found that these products were extracted into chloroform. Therefore the results of the extractions of these metal picrates are invalid and are not included in the reported results in tables 20 to 40.

Binding Agent	*Metal cation*	*% extraction*
338	Cd^{2+}	ND
	Co^{2+}	ND
	Cu^{2+}	9.79
	Sr^{2+}	ND
	Pb^{2+}	4.38
	La^{3+}	5.32

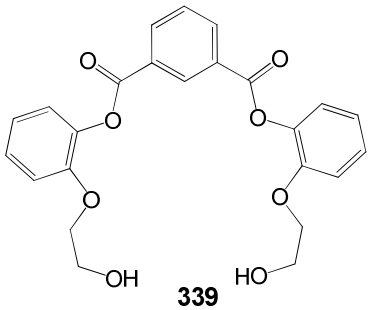
Table 20: Results of extractions with **338**



338

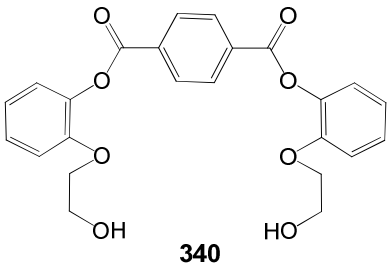
Binding Agent	*Metal cation*	*% extraction*
339	Na^{+}	2.50
	Mg^{2+}	2.61
	K^{+}	ND
	Li^{+}	4.76
	Cs^{+}	ND
	Cd^{2+}	10.35
	Co^{2+}	7.37
	Cu^{2+}	50.62
	Sr^{2+}	3.55
	Pb^{2+}	8.49
	La^{3+}	12.66

Table 21: Results of extractions with **339**



339

Binding Agent	*Metal cation*	*% extraction*
340	Na^{+}	4.85
	Mg^{2+}	ND
	K^{+}	ND
	Li^{+}	6.67
	Cs^{+}	2.64
	Cd^{2+}	3.40
	Co^{2+}	3.11
	Cu^{2+}	66.64
	Sr^{2+}	26.75
	Pb^{2+}	21.17
	La^{3+}	22.47

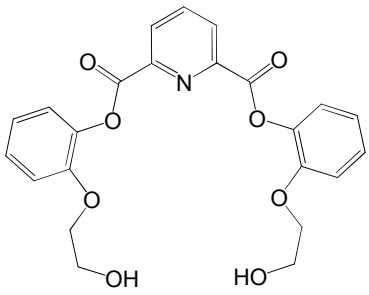


340

Table 22: Results of extractions with

340

Binding Agent	*Metal cation*	*% extraction*
341	Na^{+}	ND
	Mg^{2+}	ND
	K^{+}	ND
	Li^{+}	ND
	Cs^{+}	ND
	Cd^{2+}	21.17
	Co^{2+}	ND
	Cu^{2+}	24.76
	Sr^{2+}	ND
	Pb^{2+}	8.89
	La^{3+}	12.29



341

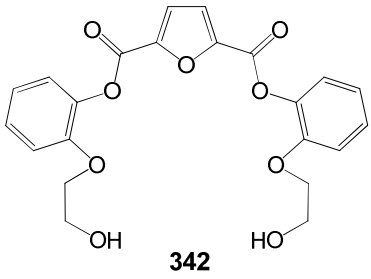
Table 23: Results of extractions with

341

Binding Agent	*Metal cation*	*% extraction*
342	Na^{+}	ND
	Mg^{2+}	ND
	K^{+}	ND
	Li^{+}	17.14
	Cs^{+}	ND
	Cd^{2+}	9.39
	Co^{2+}	5.41
	Cu^{2+}	49.28
	Sr^{2+}	9.27
	Pb^{2+}	6.11
	La^{3+}	13.16

Table 24: Results of extractions with

342

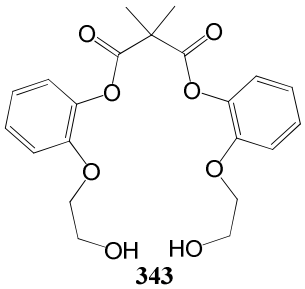


342

Binding Agent	*Metal cation*	*% extraction*
343	Na^{+}	ND
	Mg^{2+}	ND
	K^{+}	2.74
	Li^{+}	42.86
	Cs^{+}	ND
	Cd^{2+}	ND
	Co^{2+}	ND
	Cu^{2+}	63.32
	Sr^{2+}	3.55
	Pb^{2+}	5.18
	La^{3+}	10.63

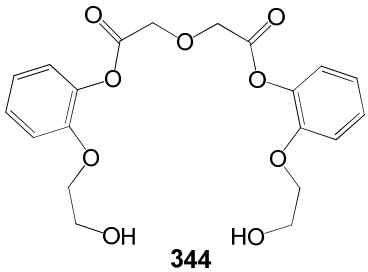
Table 25: Results of extractions with

343



343

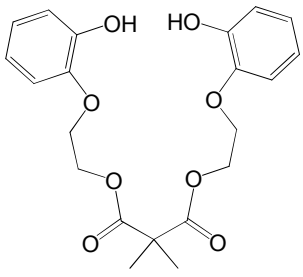
Binding Agent	*Metal cation*	*% extraction*
344	Na^{+}	2.24
	Mg^{2+}	7.47
	K^{+}	4.37
	Li^{+}	10.48
	Cs^{+}	ND
	Cd^{2+}	8.23
	Co^{2+}	14.03
	Cu^{2+}	64.19
	Sr^{2+}	7.39
	Pb^{2+}	7.03
	La^{3+}	9.21



344

Table 26: Results of extractions with **344**

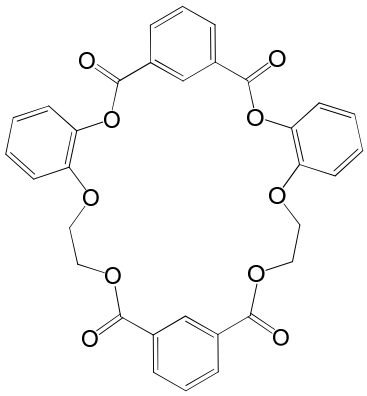
Binding Agent	*Metal cation*	*% extraction*
346	Na^{+}	ND
	Mg^{2+}	ND
	K^{+}	ND
	Li^{+}	40.00
	Cs^{+}	ND
	Cd^{2+}	12.09
	Co^{2+}	ND
	Cu^{2+}	21.26
	Sr^{2+}	2.38
	Pb^{2+}	4.91
	La^{3+}	6.13



346

Table 27: Results of extractions with **346**

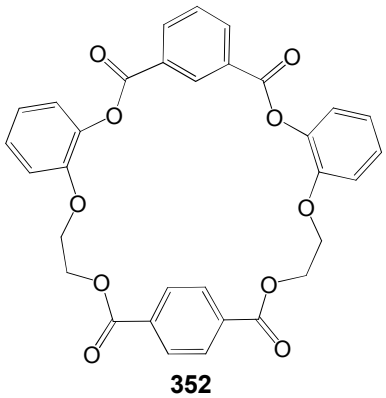
Binding Agent	*Metal cation*	*% extraction*
351	Na^{+}	ND
	Mg^{2+}	6.72
	K^{+}	3.59
	Li^{+}	ND
	Cs^{+}	ND
	Cd^{2+}	13.06
	Co^{2+}	ND
	Cu^{2+}	48.81
	Sr^{2+}	ND
	Pb^{2+}	3.99
	La^{3+}	5.94



351

Table 28: Results of extractions with **351**

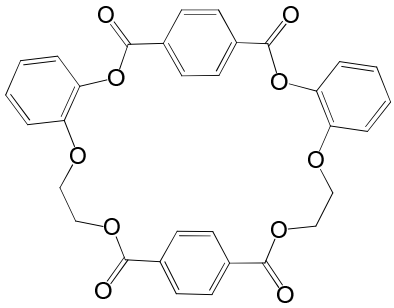
Binding Agent	*Metal cation*	*% extraction*
352	Na^{+}	ND
	Mg^{2+}	ND
	K^{+}	2.45
	Li^{+}	ND
	Cs^{+}	ND
	Cd^{2+}	ND
	Co^{2+}	ND
	Cu^{2+}	37.16
	Sr^{2+}	ND
	Pb^{2+}	ND
	La^{3+}	4.21



352

Table 29: Results of extractions with **352**

Binding Agent	*Metal cation*	*% extraction*
353	Na^{+}	ND
	Mg^{2+}	ND
	K^{+}	ND
	Li^{+}	ND
	Cs^{+}	ND
	Cd^{2+}	14.47
	Co^{2+}	ND
	Cu^{2+}	33.09
	Sr^{2+}	ND
	Pb^{2+}	4.52
	La^{3+}	5.57

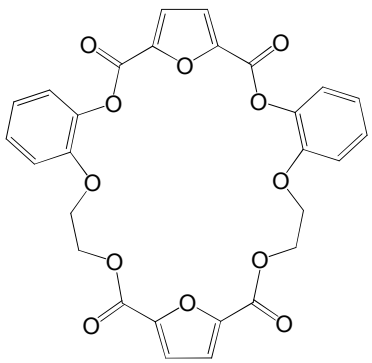


353

Table 30: Results of extractions with

353

Binding Agent	*Metal cation*	*% extraction*
354	Na^{+}	ND
	Mg^{2+}	ND
	K^{+}	ND
	Li^{+}	ND
	Cs^{+}	ND
	Cd^{2+}	ND
	Co^{2+}	ND
	Cu^{2+}	9.79
	Sr^{2+}	ND
	Pb^{2+}	ND
	La^{3+}	3.29



354

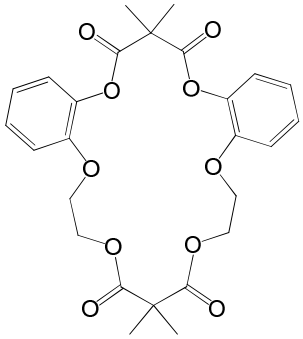
Table 31: Results of extractions with

354

Binding Agent	*Metal cation*	*% extraction*
357	Na^{+}	ND
	Mg^{2+}	ND
	K^{+}	4.16
	Li^{+}	ND
	Cs^{+}	2.42
	Cd^{2+}	17.89
	Co^{2+}	ND
	Cu^{2+}	29.01
	Sr^{2+}	ND
	Pb^{2+}	3.72
	La^{3+}	4.46

Table 32: Results of extractions with

357

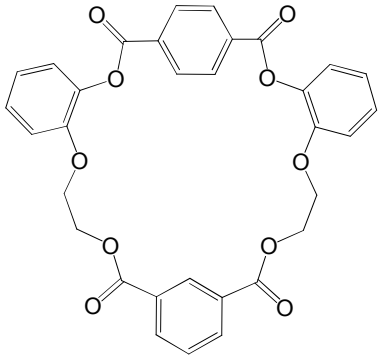


357

Binding Agent	*Metal cation*	*% extraction*
358	Na^{+}	4.59
	Mg^{2+}	3.36
	K^{+}	3.57
	Li^{+}	ND
	Cs^{+}	ND
	Cd^{2+}	12.29
	Co^{2+}	ND
	Cu^{2+}	38.91
	Sr^{2+}	ND
	Pb^{2+}	3.85
	La^{3+}	ND

Table 33: Results of extractions with

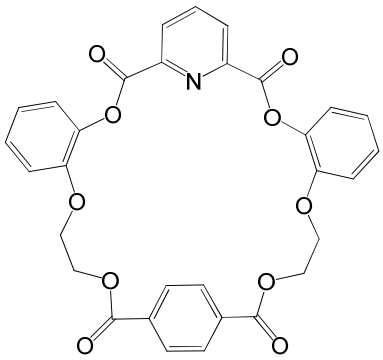
358



358

Binding Agent	*Metal cation*	*% extraction*
361	Na^{+}	25.78
	Mg^{2+}	ND
	K^{+}	13.64
	Li^{+}	ND
	Cs^{+}	10.43

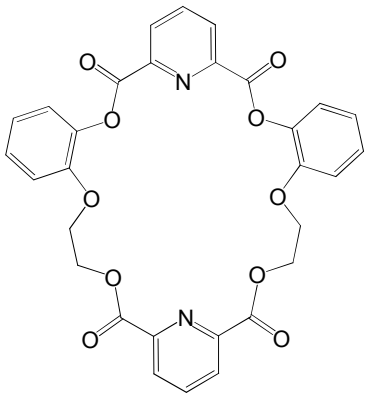
Table 34: Results of extractions with **361**



361

Binding Agent	*Metal cation*	*% extraction*
362	Na^{+}	ND
	Mg^{2+}	ND
	K^{+}	3.11
	Li^{+}	6.67
	Cs^{+}	ND
	Cd^{2+}	19.43
	Co^{2+}	ND
	Cu^{2+}	23.77
	Sr^{2+}	3.16
	Pb^{2+}	6.50
	La^{3+}	5.94

Table 35: Results of extractions with **362**

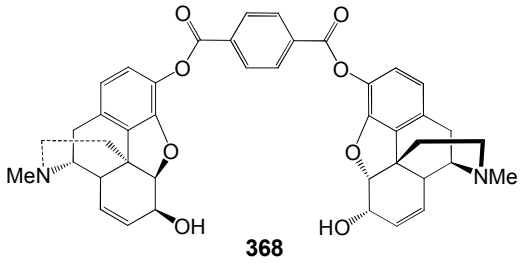


362

Binding Agent	*Metal cation*	*% extraction*
368	Na^{+}	ND
	Mg^{2+}	ND
	K^{+}	ND
	Li^{+}	ND
	Cs^{+}	17.15
	Cd^{2+}	14.02
	Co^{2+}	ND
	Cu^{2+}	ND
	Sr^{2+}	2.69
	Pb^{2+}	9.29
	La^{3+}	11.68

Table 36: Results of extractions with

368

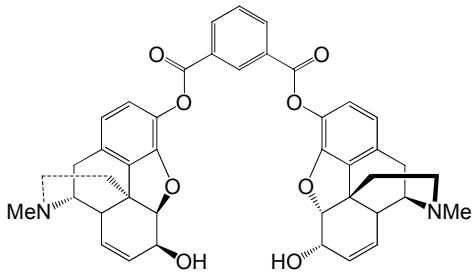


368

Binding Agent	*Metal cation*	*% extraction*
369	Na^{+}	11.79
	Mg^{2+}	2.61
	K^{+}	8.58
	Li^{+}	2.86
	Cs^{+}	26.07
	Cd^{2+}	7.84
	Co^{2+}	ND
	Cu^{2+}	ND
	Sr^{2+}	8.41
	Pb^{2+}	18.03
	La^{3+}	14.27

Table 37: Results of extractions with

369

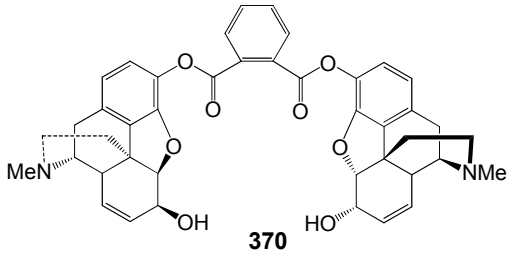


369

Binding Agent	*Metal cation*	*% extraction*
370	Na^{+}	ND
	Mg^{2+}	ND
	K^{+}	17.54
	Li^{+}	4.76
	Cs^{+}	20.63

Table 38: Results of extractions with

370

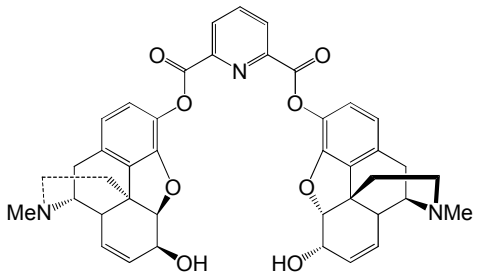


370

Binding Agent	*Metal cation*	*% extraction*
371	Na^{+}	ND
	Mg^{2+}	ND
	K^{+}	12.32
	Li^{+}	ND
	Cs^{+}	8.46
	Cd^{2+}	12.87
	Co^{2+}	ND
	Cu^{2+}	ND
	Sr^{2+}	ND
	Pb^{2+}	ND
	La^{3+}	3.47

Table 39: Results of extractions with

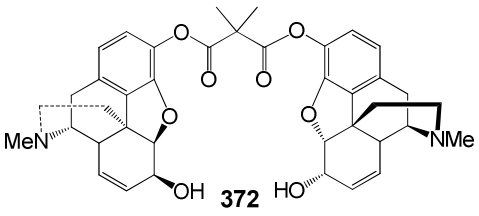
371



371

Binding Agent	*Metal cation*	*% extraction*
372	Cd^{2+}	ND
	Co^{2+}	ND
	Cu^{2+}	ND
	Sr^{2+}	5.90
	Pb^{2+}	5.97
	La^{3+}	10.01

Table 40: Results of extractions with **372**



372

Pedersen reported extraction values for crown ethers with various ring sizes and incorporating both cyclohexyl and benzene rings. The general conclusion according to the Table 41 is that crown ethers with benzene rings are more rigid and less flexible than their cyclohexyl analogues; therefore macrocycles with the same cavity size but with carbocyclic rings would extract the same metal picrate with different efficacies.

Crown Ether	Picrate Extracted			
	Li^+	Na^+	K^+	Cs^+
Dicyclohexyl-14-crown-4	1.1	0	0	0
Cyclohexyl-15-crown-5	1.6	19.7	8.7	4.0
Dibenzo-18-crown-6	0	1.6	25.2	5.8
Dicyclohexyl-18-crown-6	3.3	25.6	77.8	44.2
Dicyclohexyl-21-crown-7	3.1	22.6	51.3	49.7
Dicyclohexyl-24-crown-8	2.9	8.9	20.1	18.1

Table 41: Extraction results, two-phase liquid extraction: dichloromethane and water

The macrocycles and their precursors reported in this thesis contain two or more aromatic rings or rigid morphine units. Therefore minimal flexibility and minimal conformational change is expected on binding to the metal cation; making binding more entropically favourable. Additionally, they contain carbonyl groups which are not present in the crown ethers Pederson tested, the presence of these groups can change the electron density within the ring and as such effect the metal binding ability.

Among the compounds tested two macrocycles and four open structures, compounds **358**, **361, 339**, **340**, **344** and **369**, showed significant extraction values for sodium picrate. The two macrocycles **358** and **361** are 25 membered rings, with 6 oxygen atoms in the ring, 4 carbonyl groups and 4 aromatic groups on the ring, also **361** has a nitrogen atom. Pedersen's crown ethers dibenzo-18-crown-6 and dicyclohexyl-18-crown-6 exhibit higher affinity towards K^+ over Na^+. The same trend was observed for macrocycles with bigger cavities, dicyclohexyl-21-crown-7 and dicyclohexyl-24-crown-8, whereas binding studies performed for this project showed the opposite for macrocycle **361** with a higher affinity for Na^+ and the results for **358** are within error of each other. The results for the open structures will be compared to corresponding macrocycles later in this chapter for the possibility of utilisation of the metal carbonates as templates for the macrocyclisation reaction.

There are six macrocycles, **351**, **352**, **357**, **358**, **361** and **362**, and five precursors, **343**, **344**, **369**, **370** and **371**, that successfully extracted potassium picrate from the aqueous solution. **370**, *bis*(3-morphinyl)phthalate, extracted the highest percentage of potassium picrate from the aqueous layer. Of the macrocycles that extracted potassium picrate the most active was compound **361**, which also extracted a higher percentage of sodium and zinc, than of potassium, and successfully extracted barium, calcium and caesium to approximately the same extent as it extracted potassium. None of the macrocycles that extracted the potassium exhibited signs of selectivity for potassium, each showed higher extraction values for other metal picrates.

Lithium picrate was only extracted by one macrocycle, **362**, but this macrocycle also extracted several other metal picrates including zinc and barium, both of which it extracted more strongly. It was also extracted by eight precursors, compounds **339**, **340**, **342**, **343**, **344**, **346**, **369** and **370** to varying degrees. Of the nine compounds that extracted lithium picrate compounds **343** and **346** extracted it most effectively, both compounds within error of each other, at 42.86 % and 40.00 % respectively.

357 and **361** are the only two macrocycles that successfully extracted caesium picrate; it was also extracted by the precursors **340**, **368**, **369**, **370** and **371**. Both macrocycles that extracted caesium picrate also extracted other metal picrates at equal or higher percentage extraction. Of the seven compounds that extracted caesium picrate, **369** extracted it most effectively with a result of 26.07 % extraction. **369** extracted other picrates but of the metals tested it extracted caesium most strongly.

Magnesium picrate was extracted by two macrocycles, **351** and **358**, and by three precursors, **339**, **344** and **369**. It was most strongly extracted by **344**, with 7.47 % extraction recorded, although this is within error of the extraction recorded for macrocycle **351** which was shown to have an extraction value of 6.72. Both of these compounds extracted other metal picrates more effectively with larger extraction values being recorded for calcium and barium picrates by both compounds.

Cadmium picrate was successfully extracted by fourteen compounds, nine precursors (**339**, **340**, **341**, **342**, **344**, **368**, **369**, and **371**) and five macrocycles (**346**, **351**, **353**, **357**, **358** and **362**). The extraction values with each of the compounds were almost all between 10 % and 20 %, with the highest value being 21.17 % and the lowest being 3.40 %. Although it was successfully extracted by many of the compounds tested it was not the most strongly extracted metal picrate by any of these compounds.

Cobalt picrate was not extracted by any of the macrocycles that were tested for its extraction, although it was extracted with four macrocycle precursors, (**339**, **340**, **342** and **344**). **344** was the only compound to extract the cobalt picrate by more than 10 % with a percentage extraction of 14.03 % being recorded, although this same compound did extract other metal picrates more effectively. Similarly each of the other compounds that extracted this metal picrate extracted other metal picrates more strongly.

Fifteen compounds tested successfully extracted copper(II) picrate to varying degrees. Of these fifteen compounds eight were precursors (**338**, **339**, **340**, **341**, **342**, **343**, **344** and **346**) and six were macrocycles (**351**, **352**, **353**, **354**, **357**, **358** and **362**). Each of these compounds also extracted other metal picrates. Although **352** did not extract the copper(II) picrate most effectively, giving a value of 37.17 % compared to 66.64% for **340**, it only extracted two other metal picrates, potassium picrate (2.45 %) and lanthanum picrate (4.21 %), from the aqueous solution. This shows that **352** has a strong degree of preferential binding to copper(II) over each of the other metals tested, although in mixed solution testing it may differ. The binding of **352** to the copper(II) picrate is of interest because copper(II) has been shown to be useful as a catalyst.[76] Although other products synthesised were found to extract copper(II) picrate to a higher degree, **352** was the product which extracted copper(II) most preferentially over the other metal picrates, with almost tenfold more copper(II) picrate being extracted over the other metal picrates. This could be advantageous in the isolation of the catalyst at the end of the catalysed reaction and also in increasing the amount of

copper(II) in the organic solution, as copper(II) will not be very soluble in organic media but will be more soluble in the organic media if in a host-guest complex.

Strontium picrate was extracted by **339**, **340**, **342**, **343**, **344**, **346**, **362**, **368**, **369** and **372**. Only one of these, **362**, is a macrocycle, the rest being precursors. Of these compounds all but one extracted less than 10 %, with **340** being the only compound that extracted more, extracting 26.75 %, although **340** did not appear to be selective for strontium as it extracted a higher percentage of copper.

Sixteen compounds, **338**, **339**, **340**, **341**, **342**, **343**, **344**, **346**, **351**, **353**, **357**, **358**, **362**, **368**, **369** and **372**, extracted lead picrate to differing extents, with **340** extracting the highest percentage of it at 27.17 %. The only other compound to extract lead picrate by more than 10 % was **369**. None of the compounds, either the macrocycles (**351**, **353**, **357**, **358** and **362**) or the precursors (**338**, **339**, **340**, **341**, **342**, **343**, **344**, **346**, **368**, **369** and **372**) showed selectivity for lead picrate, each one showing either higher or similar extraction of other metal picrates.

There were nineteen compounds that extracted lanthanum picrate, six macrocycles (compounds **351**, **352**, **353**, **354**, **357** and **362**) and thirteen precursors (**338**, **339**, **340**, **341**, **342**, **343**, **344**, **346**, **368**, **369**, **371** and **372**). Of these, **340** extracted the highest percentage (22.47 %) but as before this compound also successfully extracted other metal picrates to a similar or better extent. None of the nineteen compounds showed selectivity of lanthanum picrate, they each extracted other metal picrates to a higher or similar extent.

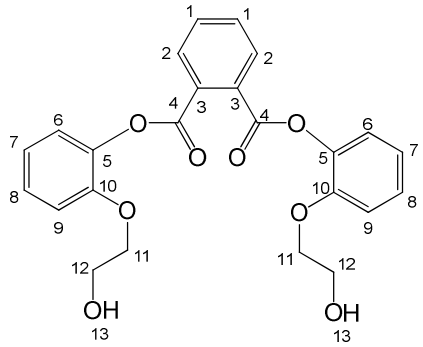
4.2.2: Metal Picrate Extraction with NMR Tests

Seven of the compounds, two macrocycles and five precursors, had their best results, from section 4.2.1, repeated with a variation on the above method in an attempt to obtain an NMR of the host-guest species. Also a selection of the negative results, at least one negative result for each compound, had the same test run on them to ensure the compounds were not degrading when subjected to the test conditions. In an effort to promote binding of the metal picrate to the macrocycle or precursor to its maximum level a saturated solution of the metal picrate in water was used in the extraction. Also the concentration of the extracting compound was increased to 15 mM so that there was enough of the compound in each extraction to obtain a good quality NMR spectrum.

Extractions were carried out as before, 6 mL of picrate solution shaken with 6 mL of macrocycle/precursor solution. All mixtures were shaken on an automatic shaker for ten minutes at 600 oscillations per minute. The mixtures were allowed to settle for ten minutes and then separated. Previously the aqueous layer had its absorbance recorded and the data used to calculate the percent extraction, by this method the organic layer was removed and the solvent evaporated *in vacuo*. The solid was then dissolved in deuterated chloroform and its NMR spectrum recorded, as it was the aim of this section to prove extraction was taking place by recoding an NMR of as many of the host-guest species as possible and not to recalculate the percentage binding. The NMR spectrum of each of the host molecules (being tested by this method) was recorded in deuterated chloroform on the same day for comparison.

Each of the recorded spectra of the product/metal picrate mixes in which no extraction was recorded (tables 20 to 40) showed no degradation of the products; with each spectrum after attempted extraction of the metal picrate matching that of the macrocycle or precursor prior to attempted extraction.

338 had the test carried out with cadmium, strontium and copper. No difference was observed in the NMR spectra from the cadmium and strontium extractions, this was the expected result. For the extraction of copper(II) picrate using this compound there was a change in the NMR. This change in chemical shift varies depending on the peak being looked at with some increasing and others decreasing by varying degrees. This degree and direction of change can be caused by both the change in electro-negativity of the atoms (by attraction of electron density by the copper(II) cation) and also by conformational changes as shown by Lee *et al*.[77] In table 42 below the differences for each of the peaks in the proton and carbon NMR spectra between compound **338** and compound **338** after extraction with copper(II) picrate are listed. Figures 100 and 101 show the proton and carbon NMR spectra respectively, of the host-guest complex. Figure 100a and 101a show the proton and carbon NMR spectra respectively, of the free host **338**, for visual comparison.



Atom Number	**338** ^{1}H NMR	**338** ^{1}H NMR After Copper(II) Extraction	Difference (ppm)	**338** ^{13}C NMR	**338** ^{13}C NMR After Copper(II) Extraction	Difference
1	7.630	7.636	+0.006	131.88	131.87	-0.01
2	7.969	7.9703	+0.004	129.73	129.76	+0.03
3				131.57	131.61	+0.04
4				165.46	165.43	-0.03
5				139.65	139.60	-0.05
6	7.160	7.164	+0.004	121.11	121.13	+0.02
7	6.903	6.907	+0.004	122.75	122.74	-0.01
8	7.095	7.093	-0.002	127.37	127.39	+0.02
9	6.950	6.954	+0.004	113.60	113.55	-0.05
10				150.40	150.38	-0.02
11	4.037	4.039	+0.002	70.36	70.38	+0.02
12	3.715	3.709	-0.006	61.05	61.03	-0.02

Table 42: Differences in carbon and proton NMR spectra of **338** *and* **338***-Cu host-guest complex.*

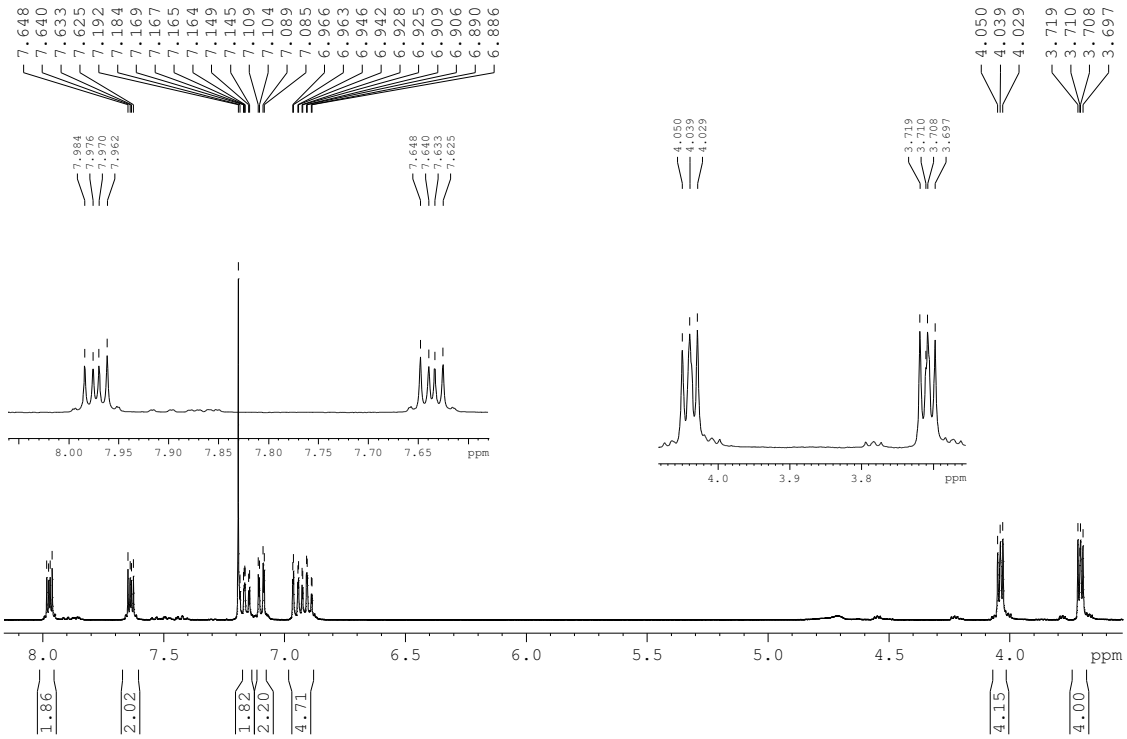


Figure 100: Proton NMR of the host-guest complex **338** *and Cu(II).*

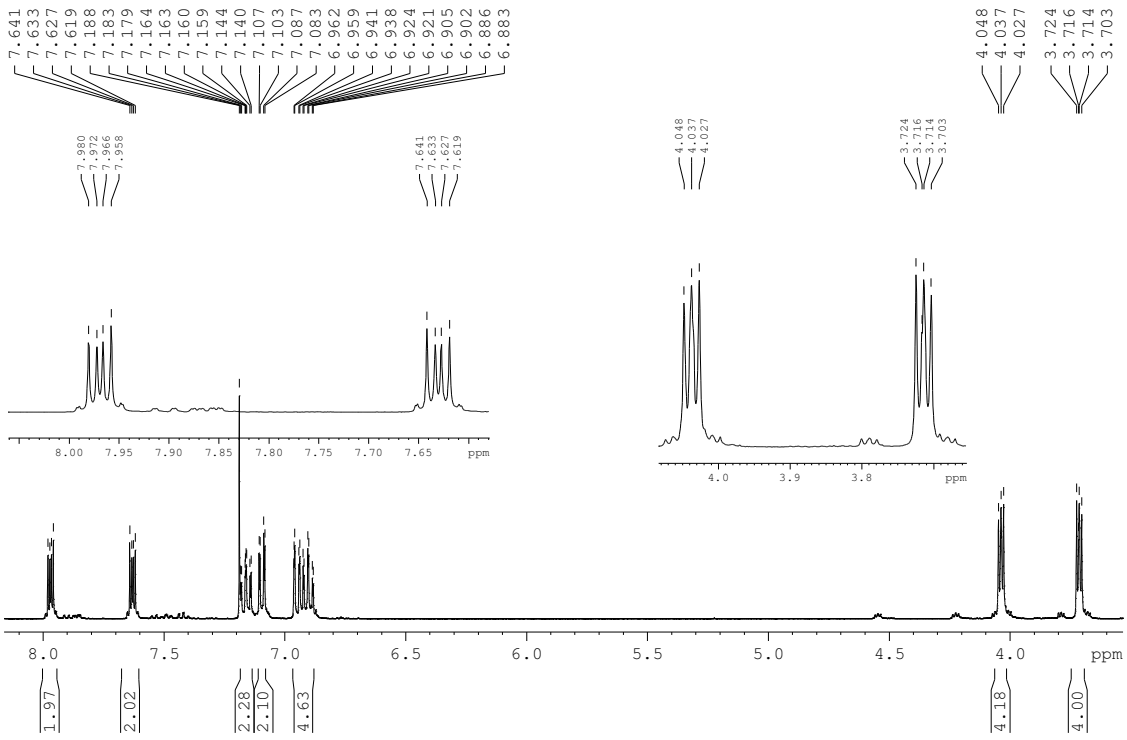


Figure 100a: Proton NMR of the free host **338**.

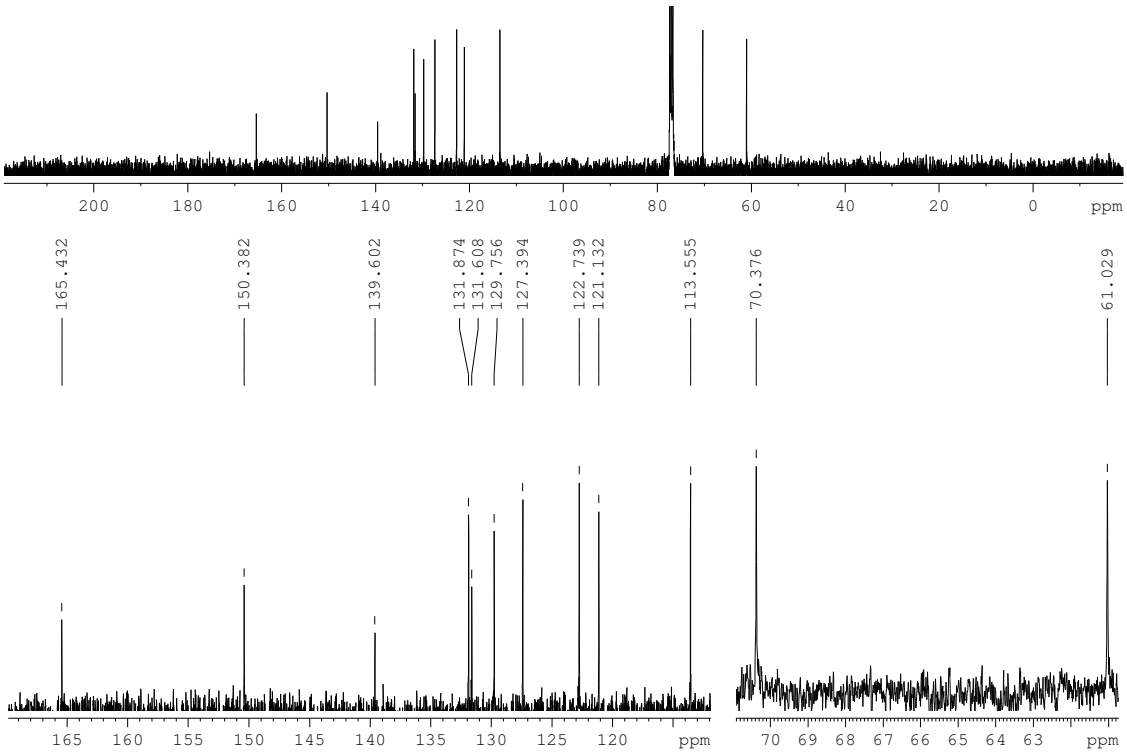


Figure 101: Carbon NMR of the host-guest complex **338** *and Cu(II).*

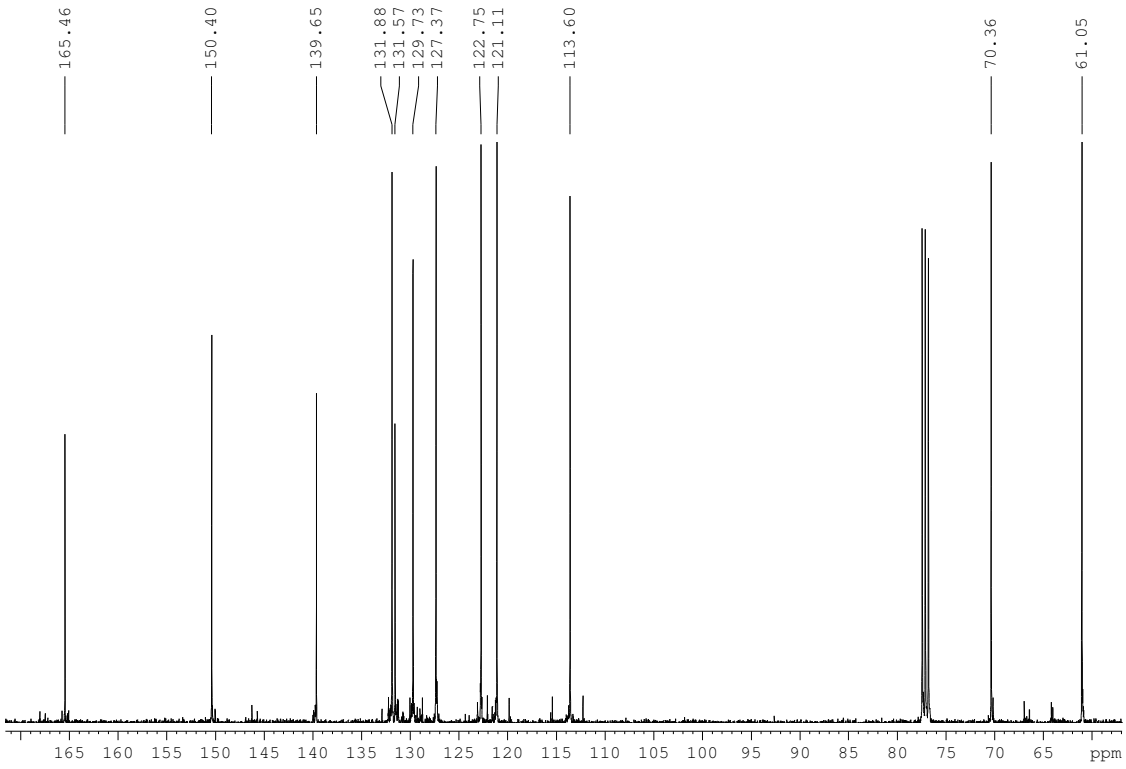


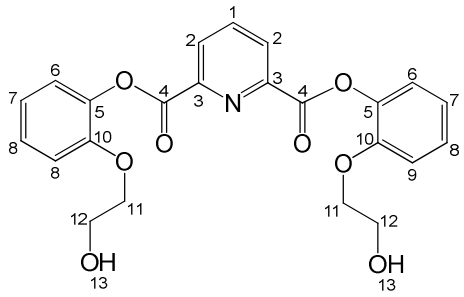
Figure 101a: Carbon NMR of the free host, **338***.*

The differences in the NMR spectra, both proton and carbon, between **338** (host) and **338** with copper(II) (host-guest complex) being relatively small, so it was decided to test the variation that can occur within the NMR of **338**. This was carried out by repeating the NMR of this compound, made up originally at 90 mM, in triplicate and

also making up three solutions, with varying concentration, for NMR and repeating the recording of these NMR spectra in triplicate also. The concentrations used were 20 mM, 40 mM and 60 mM, and each spectrum was recorded in triplicate. The maximum variation at any one peak was ±0.001 ppm in proton NMR (when zero was properly set with TMS) and ±0.01 ppm in the carbon NMR (zero also set with TMS). This procedure with varying concentrations and triplicate recording of each spectrum was carried out on each of the products tested by NMR.

The method carried out in this investigation, was not used to calculate the binding constants or percentage extraction, but instead to try to force the formation as much as possible of the host-guest complex and then to obtain an NMR of this complex showing it was different from the host in solution by itself. The differences in both proton and carbon NMR spectra is significant, being both larger than the difference in the repeated NMR spectra of **338** and also varying in magnitude and direction. If all differences were equal in magnitude and direction it would suggest that there is no significant difference as it would appear as all differences are due to incorrect zeroing of the TMS peak. It can be clearly seen from the data that the NMR spectrum of the host-guest complex of **338**-Cu^{2+} picrate has been recorded. The atoms showing the greatest change are expected to be those closest to the position of the bound metal, as the metal cation attracts electron density towards itself and away from the atoms of the macrocycle thus shifting these atoms downfield. The largest shift downfield is seen in hydrogens 1, 2, 6, 7 and 9 and in carbons 2, 3, 6 and 8 suggesting that the metal has bound to the aromatic rings withdrawing electron density from these regions.

The proton NMR of compound **341** compared to that of **341**-copper(II) picrate host-guest complex is significantly different before the location of the peaks is taken into account, as seen in figures 102 and 103.



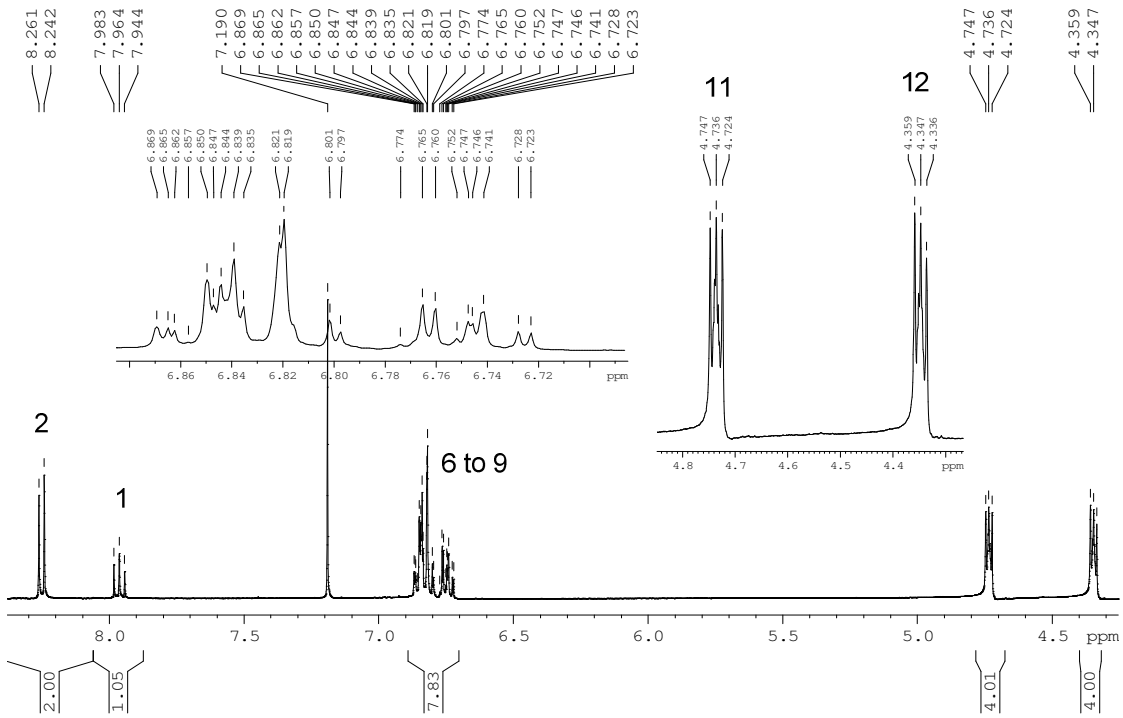


Figure 102: [1]H NMR of the host **341**.

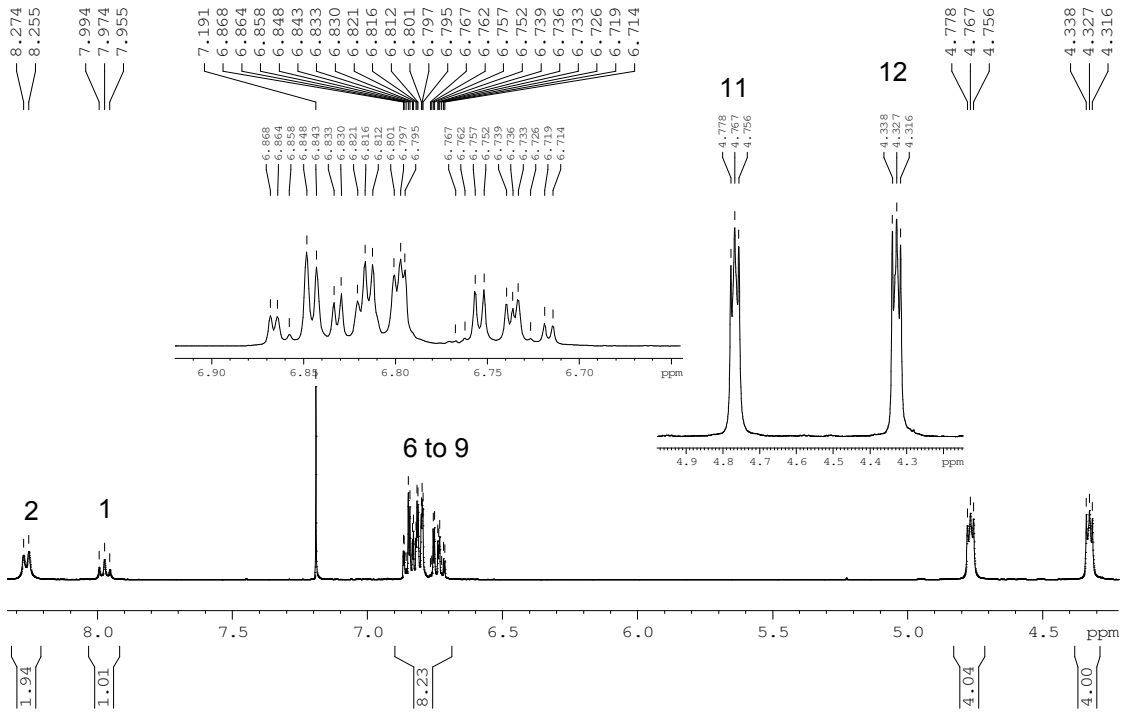
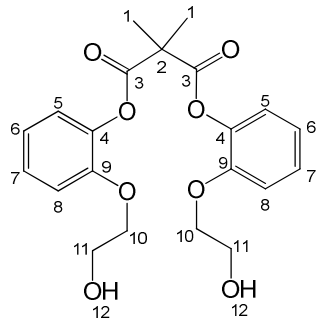


Figure 103: [1]H NMR of the host-guest complex, **341** *and Cu(II).*

As can be seen in the inset of these two figures, the region of the spectrum representing the aromatic protons (H's 6 to 9), between 6.71 ppm and 6.87 ppm, is completely different in shape, with the doublet *circa* 6.8 ppm showing greater intensity in the host-guest complex compared to the same doublet in the NMR of compound **341** by itself. This alone shows a significant difference between the two NMR spectra, but there is

also a difference of +0.031 ppm for the peak representing H11. When these two factors have been taken into account it is clear that the host-guest species of **341**-copper(II) has been formed and an NMR has clearly been recorded of it. The largest shift downfield is seen in hydrogen 11 suggesting that the metal has bound to the oxygen atom between C11 and C10. There are also changes in the phenyl rings and the pyridine ring, suggesting binding in these locations (to the aromatic rings themselves or to the hetero-atoms in and surrounding these rings). **341** also had this test carried out using sodium, magnesium, caesium and strontium picrates, each showing no significant difference from **341** after extraction, indicating no host guest complex was formed and also no decomposition of **341** took place.

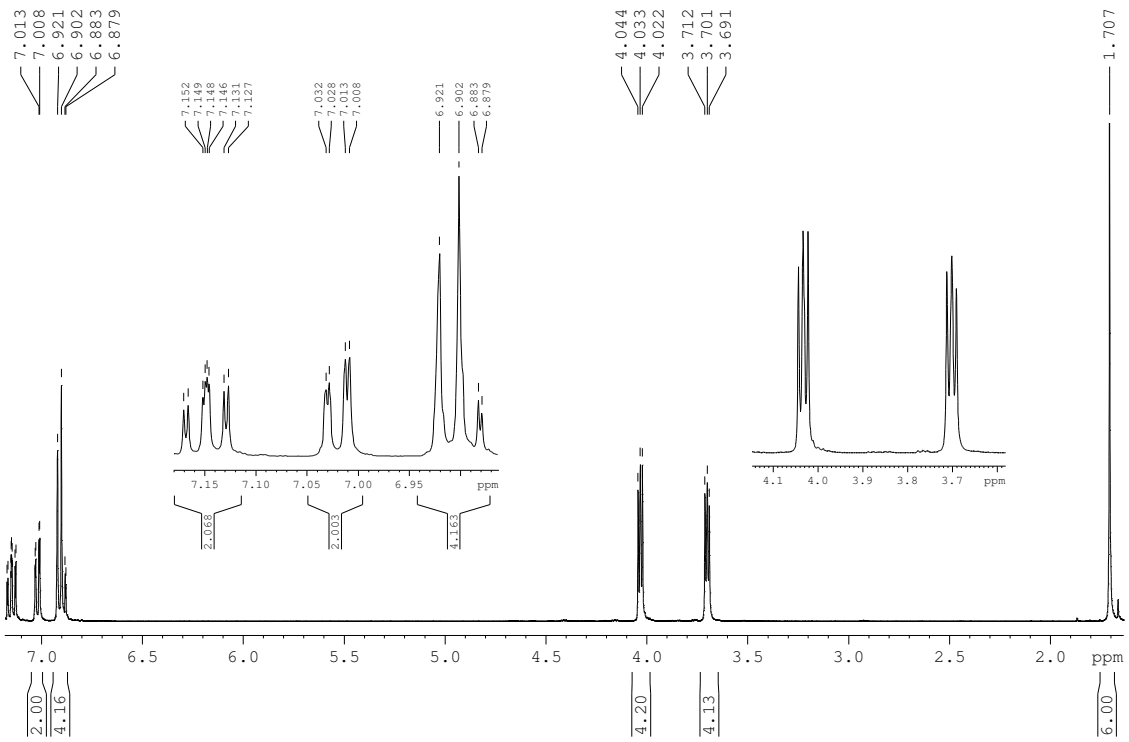
343 was also subjected to these extraction tests with lanthanum, lithium, cobalt, caesium and sodium. As expected only lanthanum and lithium showed any difference by NMR after extraction. Unlike the **341**-copper(II) host-guest complex there is no obvious visual difference between the host and host-guest complexes but there are slight differences in chemical shift. Table 43 lists the differences in the proton NMR spectra between **343** and **343** host-guest species with both lithium and lanthanum picrates.



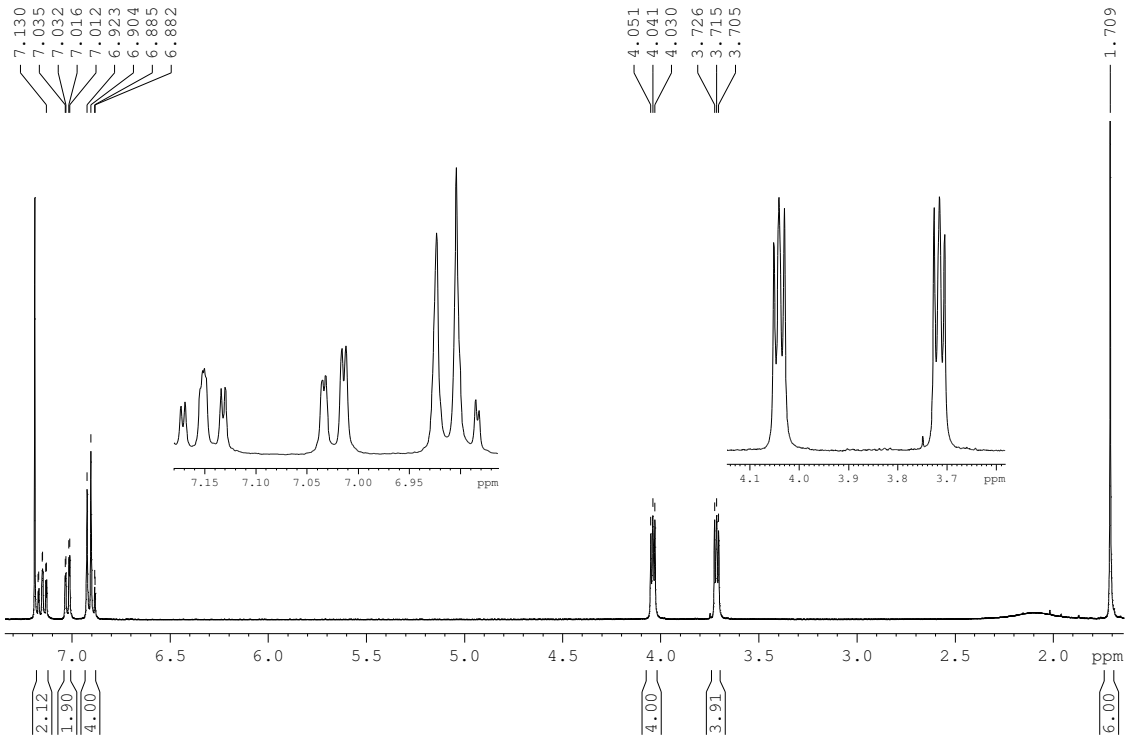
Atom Number	**343** ^{1}H	**343** ^{1}H NMR After Lithium Extraction	Difference from **343**	**343** ^{1}H NMR After Lanthanum Extraction	Difference from **343**
1	1.709	1.707	-0.002	1.707	-0.002
5	7.150	7.147	-0.003	7.148	-0.002
6	6.923-6.882	6.921-6.879	-0.0025	6.920-6.879	-0.003
7	7.024	7.021	-0.003	7.020	-0.004
8	6.923-6.882	6.921-6.879	-0.0025	6.920-6.879	-0.003
10	4.041	4.033	-0.008	4.033	-0.008
11	3.715	3.701	-0.014	3.701	-0.014

Table 43: Differences in proton NMR spectra of **343** *and* **343** *host-guest complexes.*

From the table above it can be seen that the difference in NMR between each of the host-guest species and compound **343** is approximately the same. Again in this case compound **343** had its proton NMR spectrum recorded in triplicate and also at varying concentrations, as with compound **338**. In this case there was more of a difference observed between the spectra at the same concentration, a maximum difference of 0.002 ppm seen between the NMR spectra of **338** at the same concentration. When the concentration was varied this difference was not exceeded. So although lanthanum and lithium are significantly different metals, (lanthanum is a lanthanoid and lithium is a group one metal) they appear to have the same effect on compound **343** when in a host-guest species, indicating that the binding interactions are occurring in both the same locations and to a similar strength. Figures 104 and 105 show the NMR spectra of the **343**-lithium picrate host-guest complex and the NMR of **343** for visual comparison.



Figures 104: NMR of the **343***-lithium picrate host-guest complex*



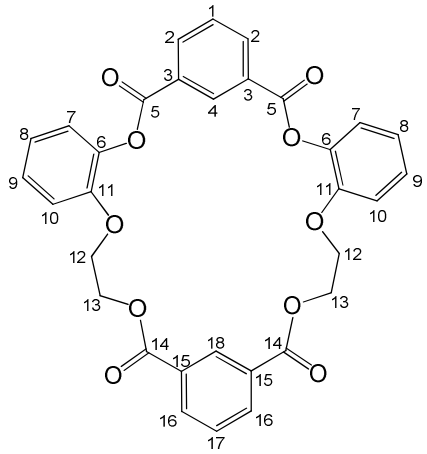
Figures 105: NMR of **343**

351 was successfully isolated in host-guest complexes with copper(II) and cadmium picrates. It was also tested with lithium, sodium, cobalt and strontium picrates, to ensure that the product did not degrade under the test conditions. As was expected, each of these did not show any host-guest complex by NMR and also no degradation of

351 was observed. Table 44 below shows the difference in the NMR spectra between compound **351** and its host-guest species with both cadmium and copper.

Atom Number	**351** ^{1}H	**351** ^{1}H NMR After Cadmium	Difference from **351**	**351** ^{1}H NMR After Copper(II)	Difference from **351**
1	7.17-7.21	7.17-7.21	0	7.17-7.21	0
2	8.159	8.151	-0.008	8.151	-0.008
4	8.375	8.385	+0.010	8.386	+0.011
7	7.351	7.342	-0.009	7.343	-0.008
8	6.97	6.97	0	6.97	0
9	7.050	7.048	-0.002	7.048	-0.002
10	6.97	6.97	0	6.97	0
12	4.305	4.304	-0.001	4.304	-0.001
13	4.623	4.617	-0.006	4.617	-0.006
16	8.022	8.018	-0.004	8.012	-0.010
17	7.17-7.21	7.17-7.21	0	7.17-7.21	0
18	8.067	8.060	-0.007	8.062	-0.005

Table 44: Differences in ^{1}H NMR spectra of **351** *and* **351** *host-guest complexes.*



There are no obvious visual differences between the NMR spectra of **351** and its host-guest complexes, as seen in figures 106 to 108. The differences in chemical shift are significant with individual peaks varying as much as ±0.01 ppm, whereas these peaks varied by only ±0.002 ppm when carrying out the NMR of **351** at varying concentrations in triplicate. The degree of change to the chemical shift of any

individual peak is indicative of the level that the guest cation affects the host in that area of the molecule thus indicating where the guest is binding in the host molecule.

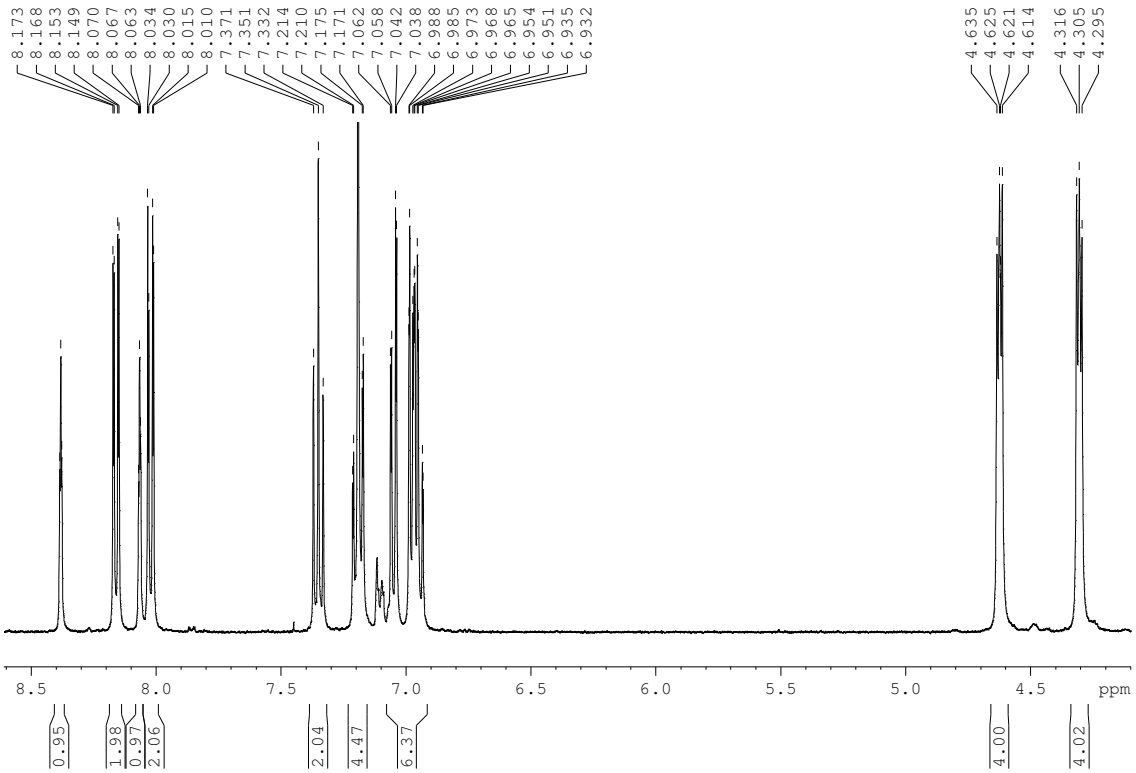


Figure 106: Proton NMR of **351**

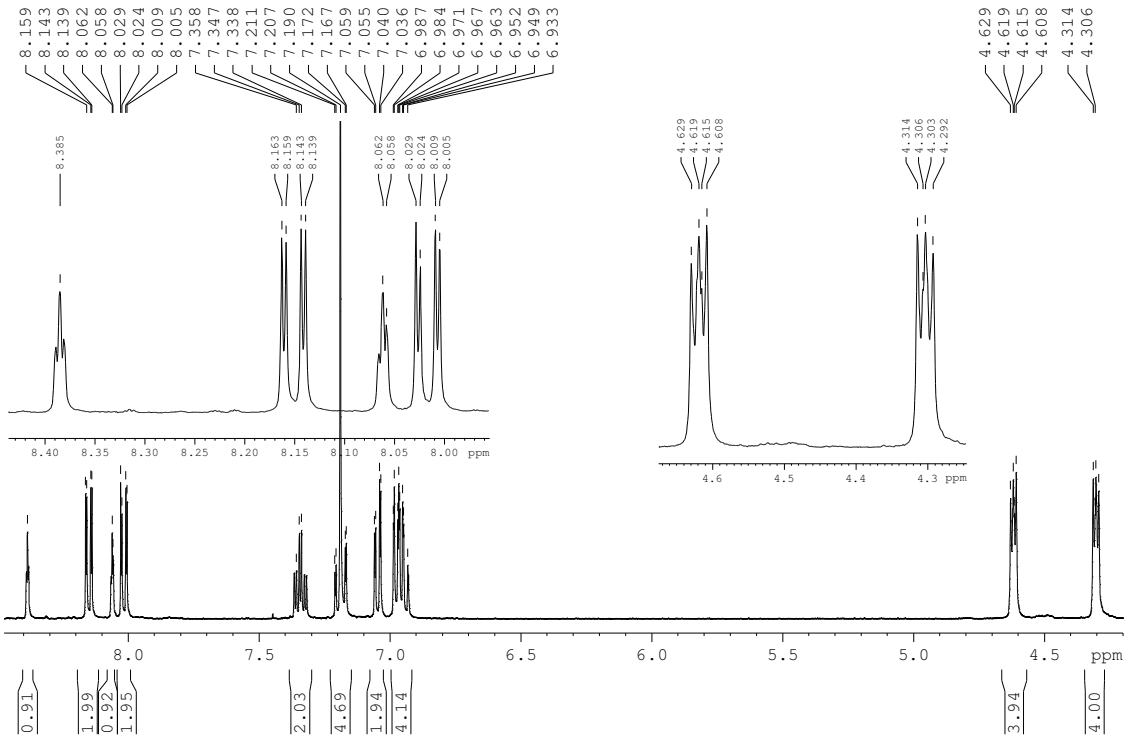


Figure 107: Proton NMR of **351**-*Cadmium(II) host-guest complex*

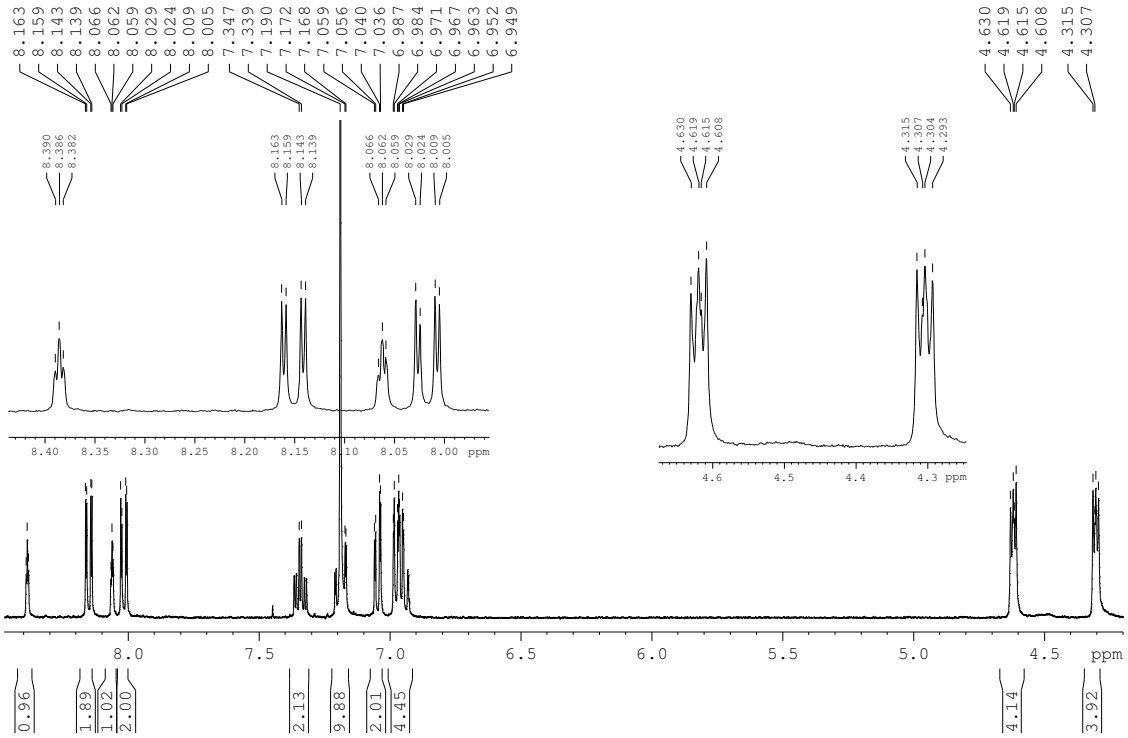


Figure 108: Proton NMR of **351**-*Copper(II) host-guest complex*

The NMR spectra of the host-guest complexes of **351** with copper(II) and cadmium are similar, thus indicating that these two metals bind to **351** in a similar manner when forming the host-guest complex. Although there are significant differences on some peaks suggesting that although the effect is similar it is not as close as is seen on the host-guest species of **343**. The biggest shift downfield was for H4 in both host guest complexes, suggesting the cationic guest has bound to the upper half of the macrocycle located in a position so as to extract most electron density from H4.

362 was successfully isolated in host-guest complexes with copper(II) and cadmium(II) picrates. It was also tested with caesium, cobalt, magnesium and sodium picrates; in each of these cases no change in the NMR was observed indicating that there was no host-guest complex formed and no degradation of the macrocycle by this extraction technique. For the host-guest species of **362** with copper(II)and cadmium there was a visual difference between the NMR spectra of the macrocycle and that of the host-guest complexes, as seen in figures 109 to 111. The visual difference is most notable in the region of the spectra between 7.9 ppm and 8.1 ppm. Here it can be clearly seen that in both host-guest species the triplet and doublet are closer together than in the spectrum for **362**. The spectrum of **362** here is different to that reported in chapter two as it is recorded in deuterated chloroform, in chapter two it was recorded

in deuterated acetonitrile, because in chloroform a solution of high enough concentration could not be made to record a carbon spectrum.

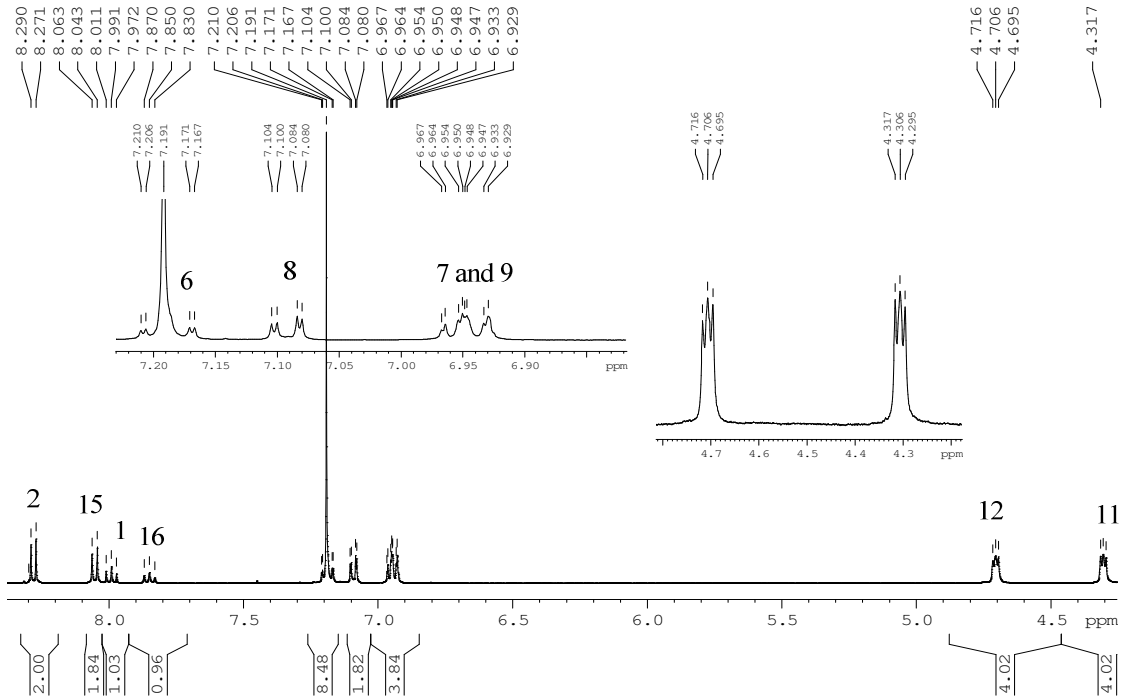


Figure 109: Proton NMR of **362**

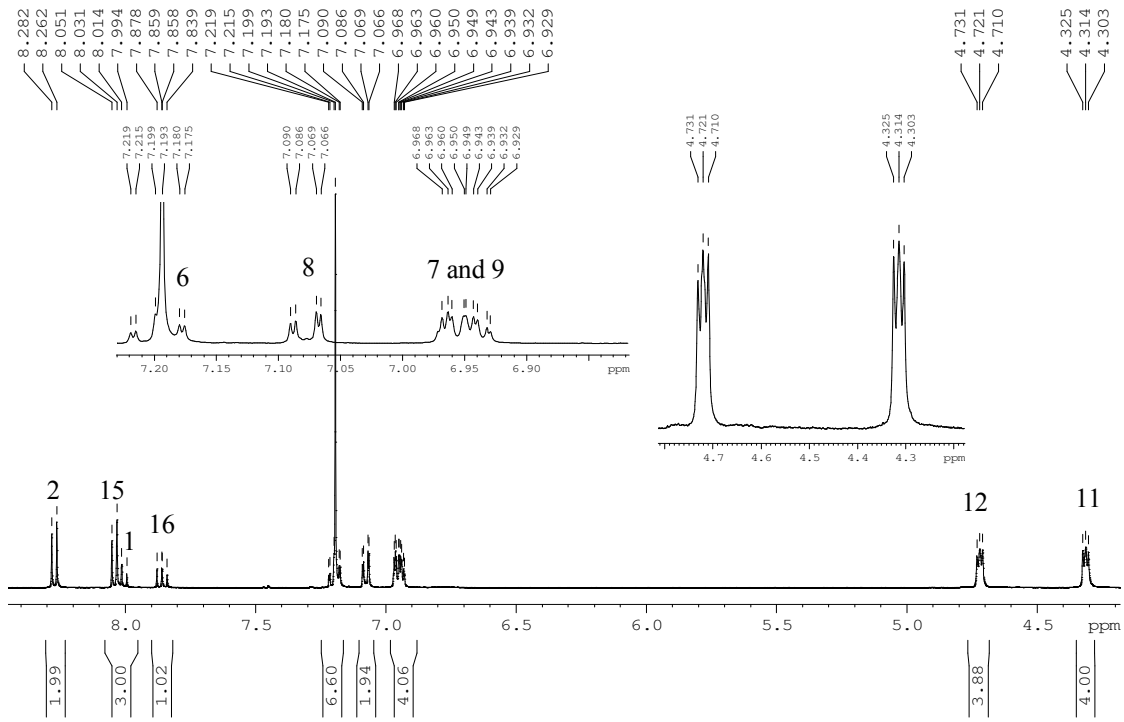


Figure 110: Proton NMR of **362***-Cadmium host-guest complex*

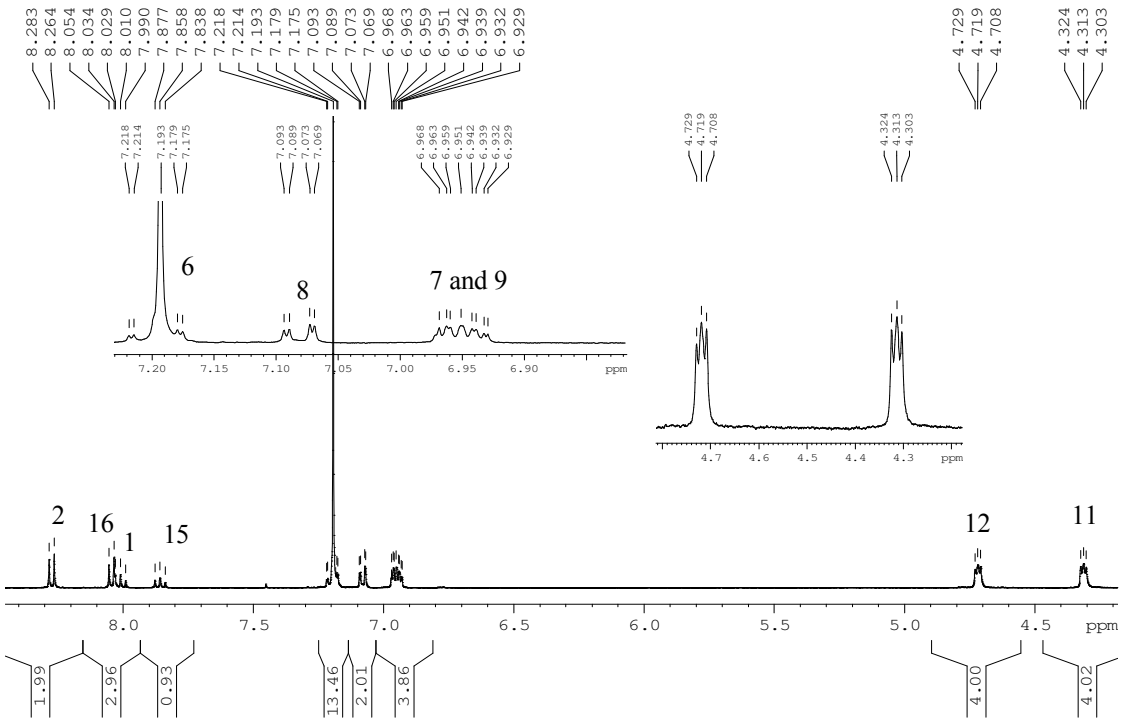
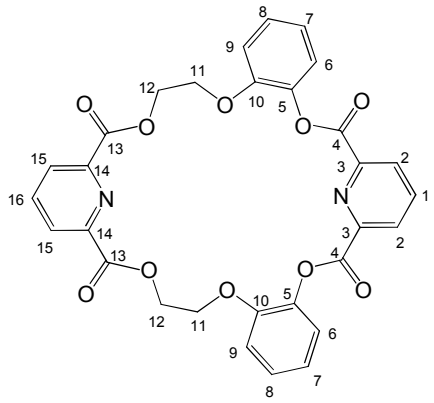


Figure 111: Proton NMR of **362**-*Copper(II) host-guest complex*

Beyond the clear visual difference between the spectra there are less obvious differences in chemical shift in the spectra which are detailed in table 45 below.



Atom Number	**362** ^{1}H	**362** ^{1}H After Cadmium	Difference from **351**	**362** ^{1}H After Copper(II)	Difference from **362**
1	7.991	8.014	0.023	8.010	0.019
2	8.280	8.272	-0.008	8.274	-0.006
6	7.167-7.210	7.175-7.219	0.008	7.175-7.218	0.008
7	6.929-6.967	6.929-6.968	0	6.929-6.968	0
8	7.092	7.077	-0.015	7.081	-0.011
9	6.929-6.967	6.929-6.968	0	6.929-6.968	0
11	4.306	4.314	0.008	4.313	0.007
12	4.706	4.721	0.015	4.719	0.013
15	8.053	8.041	-0.012	8.044	-0.009
16	7.850	7.859	0.009	7.858	0.008

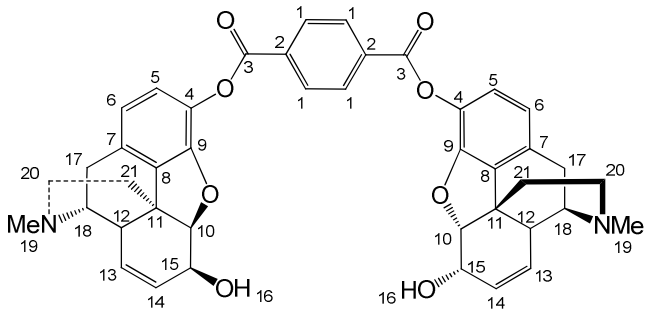
Table 45: Differences in proton NMR spectra of **362** *and* **362** *host-guest complexes.*

As can be seen both visually in figures 109 to 111 and from the data in table 45 the host-guest complexes of macrocycle **362** with both copper(II) and cadmium have been successfully identified. Each host-guest species is significantly different from **362** as a free macrocycle and they are also different from each other. The difference between each other is less apparent than the difference from the free macrocycle but it can be seen both visually when looking at the peaks from H1 and H16 and also in the data from these peaks. These two peaks are closest in the **362**-cadmium host guest species, a little further apart in the **362**-copper(II) host guest species and further apart again in the free macrocycle. The greatest shifts downfield are for hydrogens 1 and 12 and then 6, 9 and 11 in the host guest complex, this suggests that the cationic guest species are extracting electron density from areas that affect these hydrogens most strongly within the macrocycle, thus binding in these areas. This suggests that these metal cations are binding throughout the entire macrocycle rather than just in one area, extracting

electron density from both pyridine rings and each of the oxygens. Copper(II) and cadmium(II) are in the same oxidation state and have similar diameters (see table 19) so they may have the correct charge and size for efficient binding to **362**. Although cobalt(II) is only slightly smaller than copper(II), it did not show any detectable levels of extraction (table 35) which suggests that it may be too small for effective binding to **362**.

This testing was carried out with **368** in conjunction with copper, magnesium, caesium, potassium and sodium picrates. The host-guest complex of **368** with caesium has been isolated by this method; each of the other metal picrates failed to give the host-guest complex, as expected, and also did not degrade **368**.

The NMR spectra of the host-guest complex and that of **368** are significantly different, both proton and carbon. The difference in both the proton and carbon NMR spectra cannot be seen easily by visual inspection of the spectra, mainly because the NMR spectra are complicated with numerous peaks close together, as seen in figures 112 to 115. The differences are highlighted in table 46. In the carbon NMR there appears to be a peak missing in the aromatic region of the spectrum, there are also peaks at 30.95 ppm and at 207.07 ppm. The two peaks at 30.95 ppm and at 207.07 ppm correspond to acetone, which must have been residual in the NMR tube as there was no acetone used in this procedure. It appears that the peak at 130.52 ppm in the carbon NMR of the **368**-caesium host-guest complex appears to have a very high intensity and is thought to be the amalgamation of two peaks from compound **368**, those peaks being for C1 and C7, which would indicate a significant change in C7 and a less significant change in C1. There is a strong change downfield in the position of C2 which is in the same subunit as C1. There are also many other significant changes in the chemical shifts throughout the spectra which implies that there is strong binding of caesium across the entire molecule of **368**.



Atom Number	**368** ^{1}H	**368**-Caesium ^{1}H	Difference	**368** ^{13}C	**368**-Caesium ^{13}C	Difference
1	8.223	8.242	+0.019	130.50	*130.52*	+0.02
2				134.20	134.48	+0.28
3				163.22	163.23	+0.01
4				133.39	133.41	+0.02
5	6.811	6.834	+0.023	120.09	120.15	+0.06
6	6.595	6.526	-0.069	121.07	121.30	+0.23
7				131.68	*130.52*	-1.16
8				132.56	131.87	-0.69
9				148.73	148.78	+0.05
10	4.876	4.908	+0.032	58.87	59.10	+0.23
11				42.69	42.53	-0.16
12	2.543	2.768	+0.225	40.45	40.03	-0.42
13	5.732	5.768	+0.036	127.87	127.39	-0.48
14	5.247	5.261	+0.014	133.29	132.35	+0.06
15	4.119	4.136	+0.017	92.53	92.40	-0.13
17	3.307, 2.290	3.452, 2.404	+0.145, +0.114	20.77	21.00	+0.23
18	2.643	2.705	+0.062	65.86	65.74	-0.12
19	2.358	2.474	+0.116	43.13	42.91	-0.22
20	3.015, 2.290	3.051, 2.404	+0.036, +0.114	46.39	46.51	+0.12
21	2.013, 1.848	2.126, 1.906	+0.113, +0.058	35.24	34.86	-0.38

Table 46: Differences in NMR spectra of **368** *and* **368***-caesium host-guest complex.*

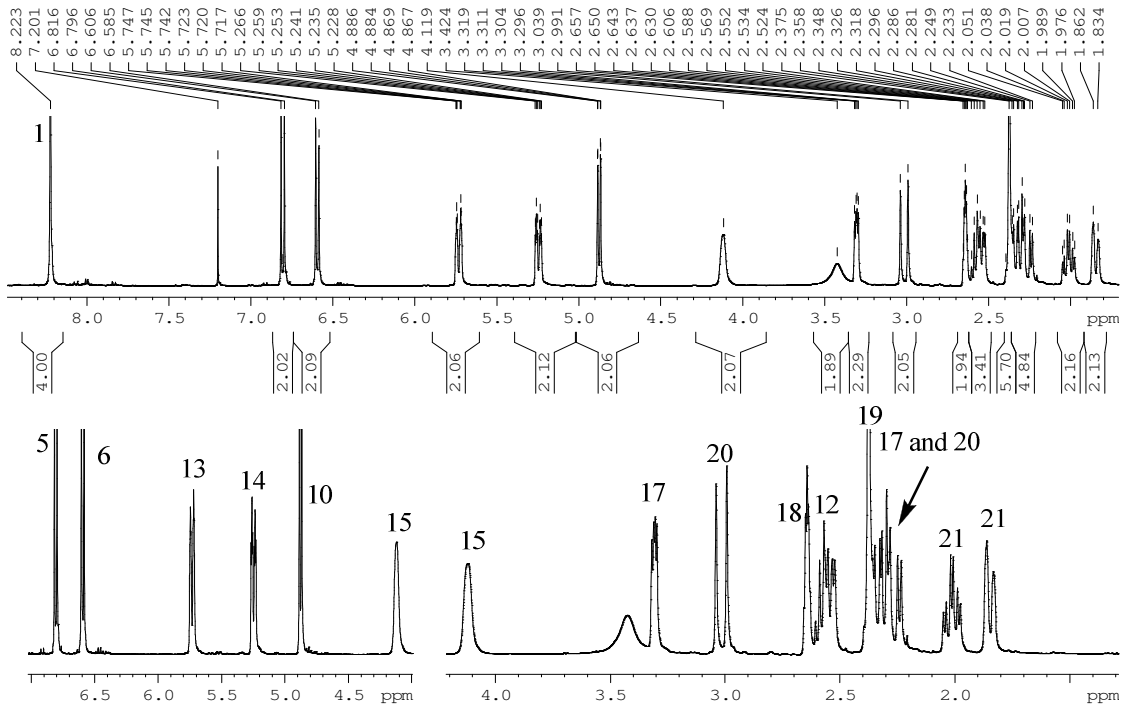


Figure 112: Proton NMR of **368**

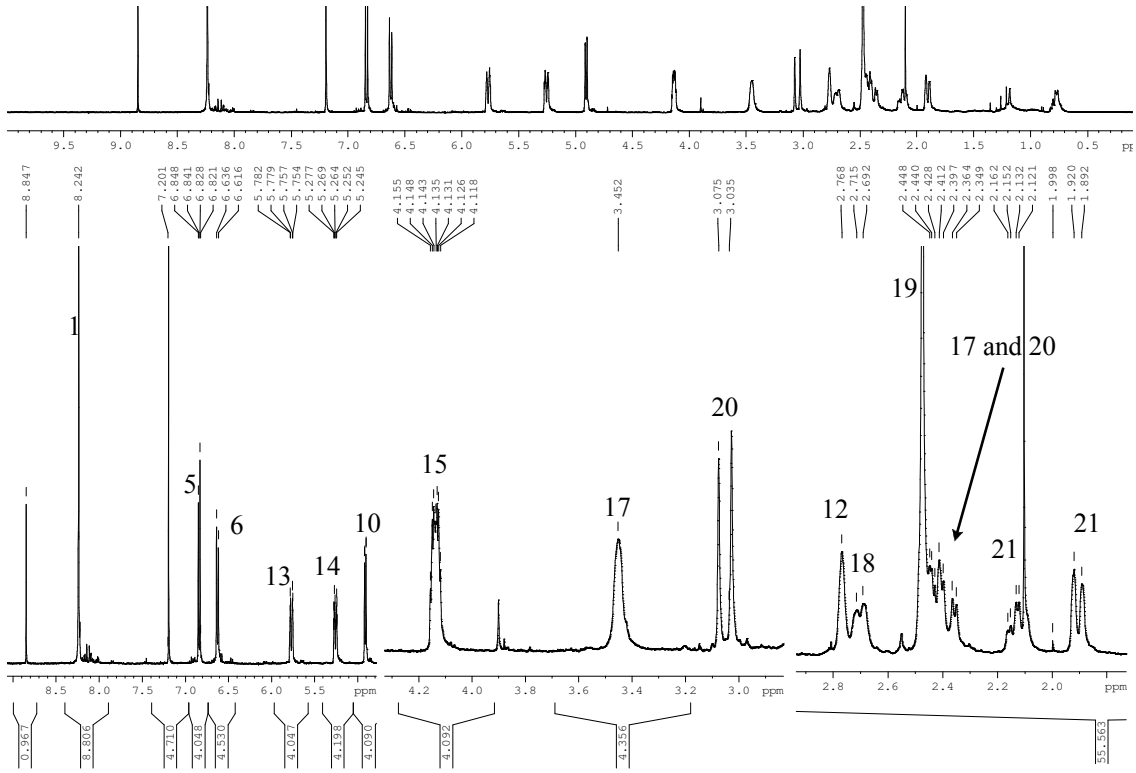


Figure 113: Proton NMR of **368***-Caesium host-guest complex*

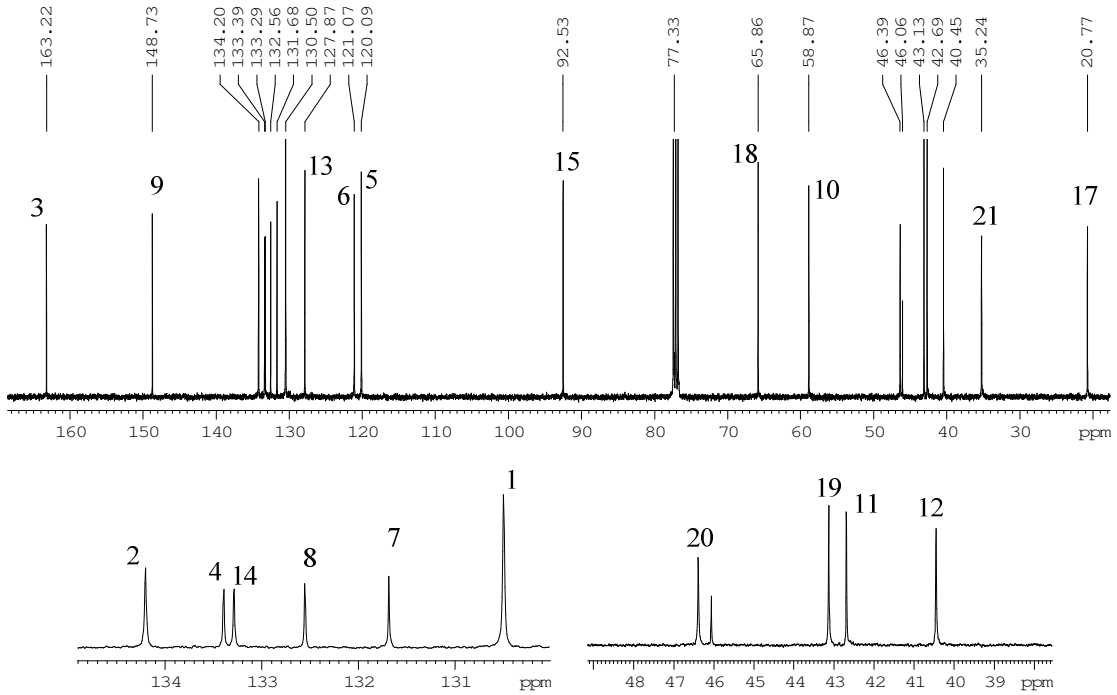


Figure 114: Carbon NMR of **368**

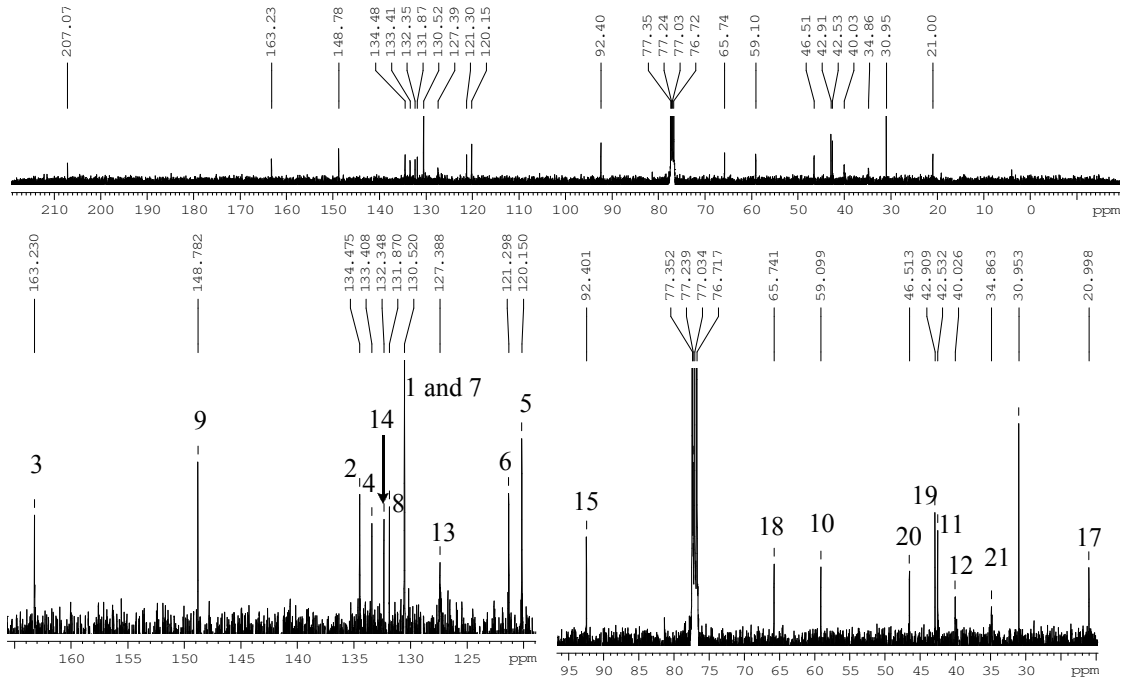


Figure 115: Carbon NMR of **368***-Caesium host-guest complex*

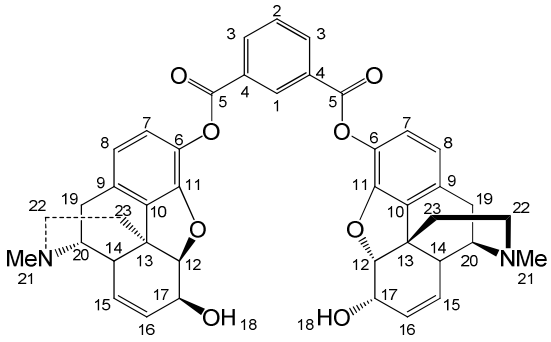
As with each of the other examples of the host-guest complexes the NMR of the host, **368**, was recorded in triplicate and at different concentrations in order to ascertain the degree of variation of the NMR spectrum of **368**. Similarly the variation on the proton NMR spectrum was ±0.002 ppm and 0.01 in the carbon spectrum. The NMR spectra, both carbon and proton, of the host-guest complex was shown to be significantly

different from that of **368**, with differences as large as +0.28 ppm to -1.16 ppm in the carbon spectra and +0.116 ppm to -0.069 ppm in the proton spectra.

This testing was carried out on **369** in conjunction with cobalt, copper, lead and lanthanum picrates. Both lead and lanthanum picrates caused changes to the spectrum of **369** after the extraction, indicating the successful binding of the cation to compound **369**. Cobalt and copper(II) picrates had no effect on the spectrum of **369** after the extraction indicating that not only was there no binding but also that **369** is stable to the extraction procedure.

The NMR spectra of each of the host-guest species not only differed from that of **369** but also from each other, as seen from table 47 and figures 116 to 118. This alludes to a differing interaction between each of these metals and **369**; the reasoning for this could be due to a number of factors, including the different nature of the metal cations, the location of binding of the metal to the host (possible binding to the nitrogen atoms, oxygen atoms, aromatic rings, or any combination of all three) and also the host to guest ratio. As with the host molecules in each of the previous host-guest species in this section the NMR of the host was recorded in triplicate and at different concentrations, and again the differences seen in the host-guest complexes far exceed those seen in the free host. As can be seen in table 47 the **369**-lanthanum complex is significantly different to unbound **369**, with the differences varying in both direction and magnitude. Also the **369**-lead complex is significantly different to metal free **369**, with one peak showing a chemical shift change in an upfield direction compared to the rest shifting downfield. Although the changes in the NMR spectrum of the **369**-lanthanum complex are varied they are not obvious on inspection of the NMR, figure 117, whereas there is a marked difference in the spectrum of the **369**-lead complex as seen in figure 118. The NMR spectrum of the **369**-lead complex shows a significant broadening of peaks in the region of 2 to 3 ppm. The cause for this is not clear. From the clarity of the spectrum across the region of 4.5 to 9 ppm it is indicated that it was not the product degrading as multiple extra peaks would have appeared across the region nor was it not a problem with the NMR spectrometer. In the ^{1}H-NMR spectrum of the **369**-Lanthanum host guest complex the change in chemical shift of the hydrogens on the isophthaloyl subunit (H's 1, 2 and 3) are less significant than the change in chemical shift for the morphine units, suggesting that the lanthanum interacts more strongly with the morphine units and more specifically the B and D rings (figure 81, chapter 3) as the hydrogens on these rings show the biggest difference in chemical

shift. With the **369**-lead host guest complex the difference in the hydrogens of the isophthaloyl subunit appear to have changed more, but with this complex the broadening of the peaks in the spectrum makes it more difficult to infer where the strongest interactions are taking place.



Atom Number	**369** ^{1}H	**369**-Lanthanum ^{1}H	Difference	**369**-Lead ^{1}H	Difference
1	8.934	8.928	-0.006	8.928	-0.006
2	7.595	7.598	+0.003	7.605	+0.010
3	8.377	8.378	+0.001	8.382	+0.005
7	6.836	6.835	-0.001	6.856	+0.020
8	6.617	6.620	+0.003	6.640	+0.023
12	4.883	4.884	+0.001	4.914	+0.031
14	2.689	2.702	+0.013	Peak to broad to determine	
15	5.759	5.762	+0.003	5.790	+0.031
16	5.249	5.253	+0.003	5.252	+0.003
17	4.134	4.128	-0.006	4.142	+0.008
19	3.427, 2.43-2.34	3.452, 2.45-2.36	+0.025, +0.02	3.575, second peak to broad to determine	+0.148
20	2.790	2.765	-0.025	Peak to broad to determine	
21	2.462	2.476	+0.014	2.558	+0.096
22	3.043, 2.43-2.34	3.048, 2.45-2.36	+0.005, +0.02	3.070, second peak to broad to determine	+0.027
23	2.125, 1.895	2.125, 1.905	0.000, +0.010	First peak to broad to determine, 1.953	+0.058

Table 47: Differences in ^{1}H NMR spectra of **369** *and* **369** *host-guest complexes*

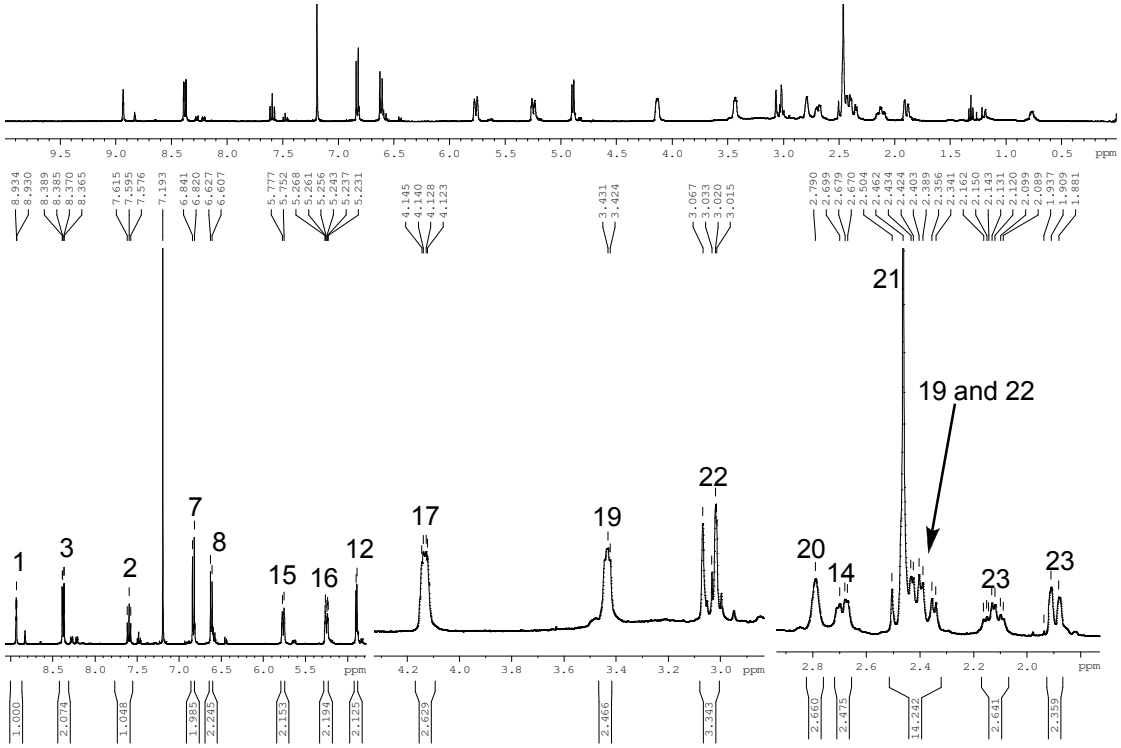


Figure 116: ^{1}H NMR of **369**

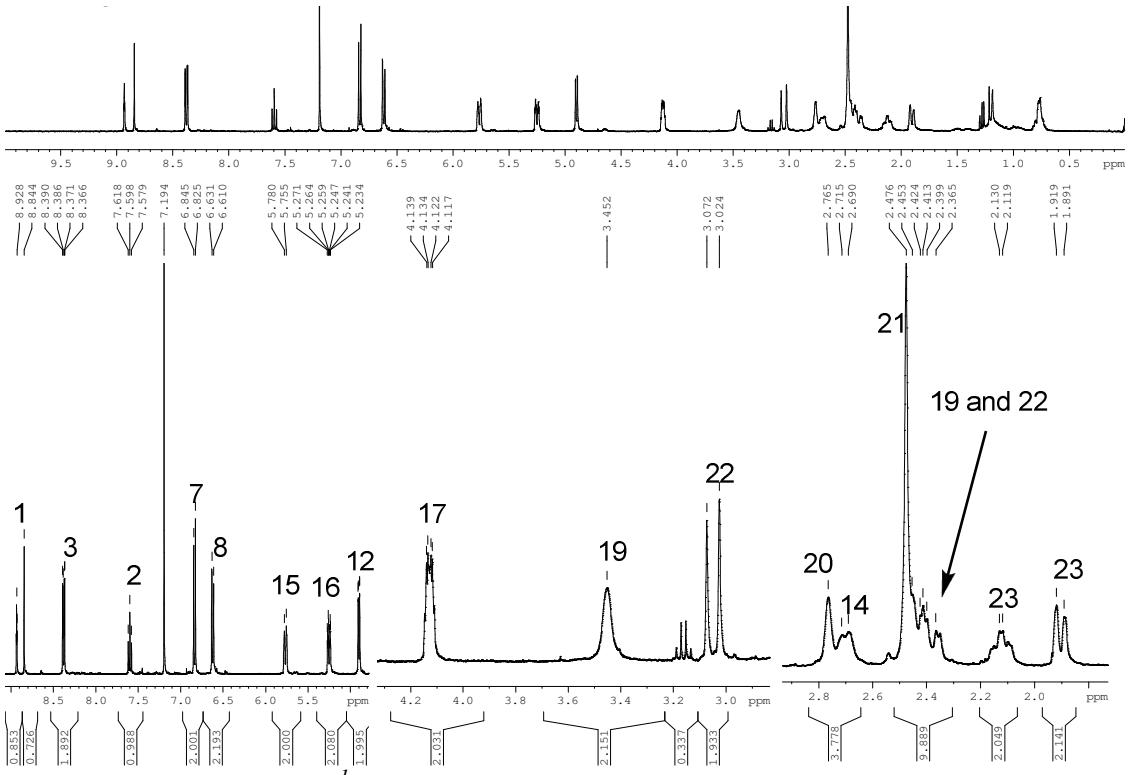


Figure 117: ^{1}H NMR of **369***-Lanthanum host-guest complex*

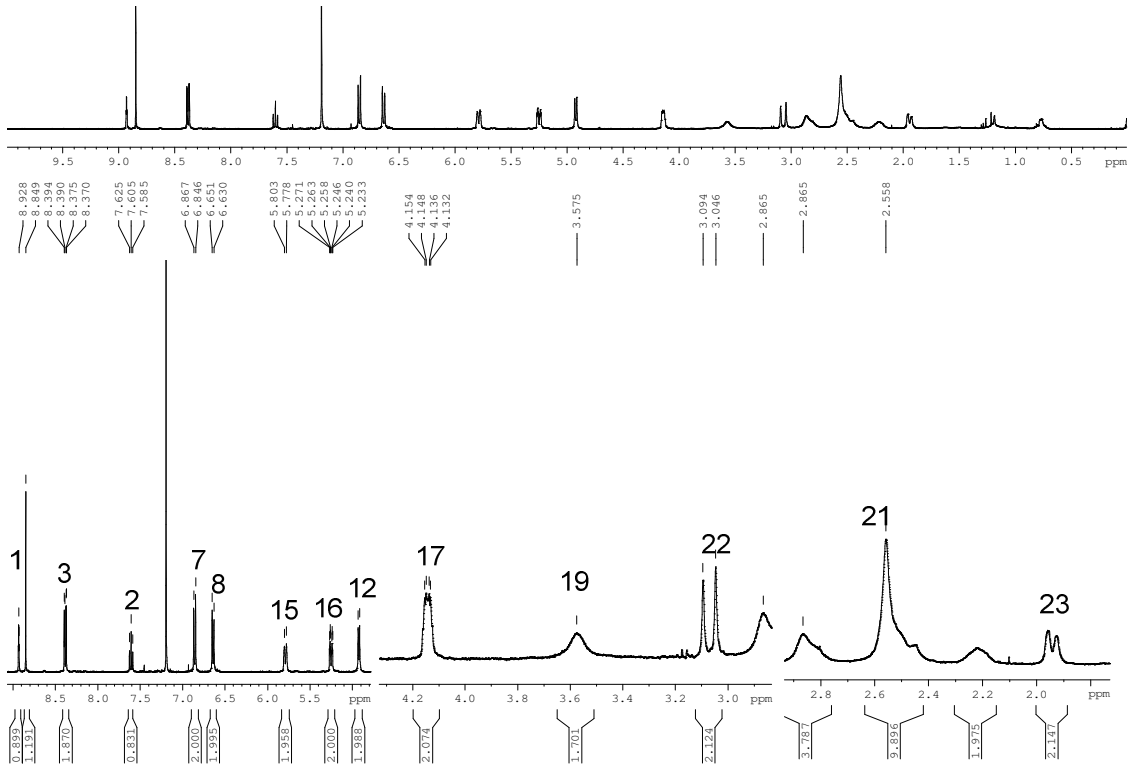


Figure 118: Proton NMR of **369***-Lead host-guest complex*

This testing has clearly shown, with seven examples that the products are stable to the extraction tests carried out here and in the previous testing, section *4.2.1* page 179. Also demonstrated herein is the ability of the products of this project to extract metal picrates from the aqueous phase into chloroform solution by binding to them, which in turn stabilises the metal cations in organic media.

4.2.3: Metal Templatation reactions

From the results obtained earlier in this chapter it was decided to attempt to synthesise the macrocycles using metal templatation reactions. Each macrocyclisation was attempted four times with the selected metal carbonate; in the presence of and absence of triethylamine as the active base and each of these (with and without triethylamine) both at room temperature and in refluxing dichloromethane. The goal of the templatation reactions was to increase the yield of the macrocycle by using a metal template in the cyclisation step which should hold the acyclic structure in a conformation in which the cyclisation step occurs more readily than without the metal template. Another viable option is to use a metal that will not bind to the acyclic structure but instead only to the macrocycle and if a large excess of this metal is present it may force the equilibrium towards the formation of the host-guest complex and hence of the macrocycle. The ideal metal template will bind to the open structure

but when the macrocycle has formed it will no longer bind giving the free macrocycle as the product rather than the host guest complex. With this ideology in mind the first series of macrocyclisation reactions to be attempted using a metal template will use metals which showed extraction to the open structures, in section *4.2.1*, but not to the corresponding macrocycles. For the purposes of this study a value of 10 % extraction was deemed acceptable as low enough extraction to be classified as not extracting, i.e. if the macrocycles (or their precursors) did not extract the metal picrate by more than 10 % it was deemed non-extracting (or non-binding) for the purposes of this set of experiments and classified in the corresponding series. The next series contained metals which were extracted both to the open structure and to the macrocycle and the final series contained metals which were extracted to the macrocycles but not by the open structures. The structures of the macrocycles being synthesised by the metal templatation method are shown in figure 119 below.

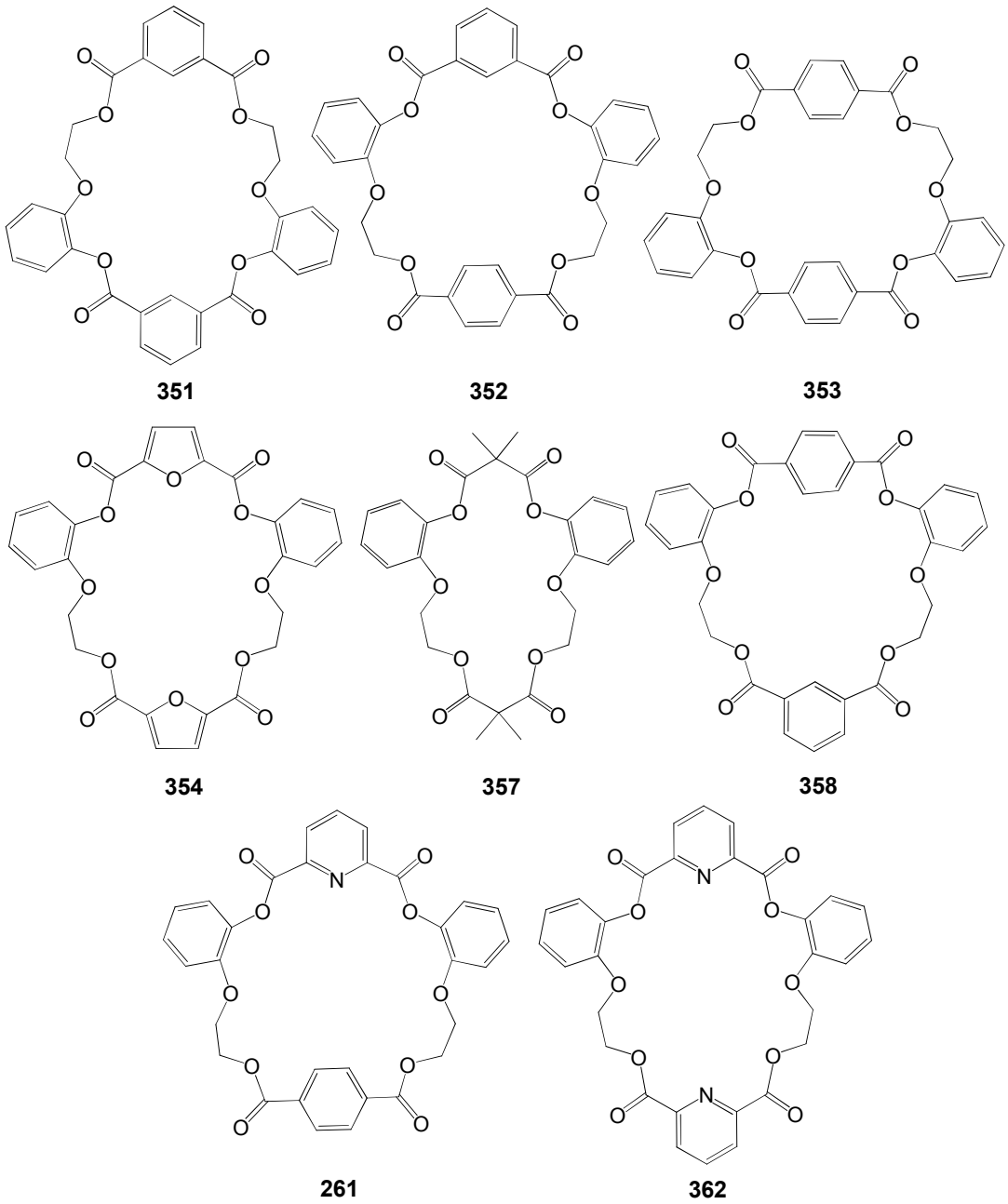


Figure 119: The macrocycles being synthesised by the metal templatation method

The combinations of macrocycle-metal attempted in each series are detailed in table 48.

Macrocycle being synthesised	Metal Carbonate used in Series 1	Metal Carbonate used in Series 2	Metal Carbonate used in Series 3
351 (from **339**)	La^{3+}	Cd^{2+}, Cu^{2+}	
352 (from **339**)	La^{3+}	Cu^{2+}	
353 (from **340**)	La^{3+}, Pb^{2+}, Sr^{2+}	Cu^{2+}	Cd^{2+}
354 (from **342**)	Cd^{2+}, La^{3+}, Li^{+}, Sr^{2+}	Cu^{2+}	
357 (from **343**)	La^{3+}, Li^{+}	Cu^{2+}	Cd^{2+}
357 (from **346**)	La^{3+}	Cd^{2+}, Cu^{2+}	
358 (from **340**)	La^{3+}, Pb^{2+}, Sr^{2+}	Cu^{2+}	Cd^{2+}
361 (from **341**)	Cd^{2+}, Cu^{2+}, La^{3+}		Cs^{+}, K^{+}, Na^{+}
362 (from **341**)	La^{3+}	Cd^{2+}, Cu^{2+}	

Table 48: The combinations of macrocycle-metal attempted in each series

The metal carbonates were dried in the oven at 120 ^{o}C for one week. Each synthesis was carried out using the appropriate *bis*-alcohol (or *bis*-phenol as in **346**) as the acyclic starting material. All syntheses were carried out in dry dichloromethane under nitrogen and at the same concentration (0.12 M) of *bis*-alcohol starting material and 6 equivalents of metal carbonate. If triethylamine was used as the base there were 2.42 equivalents were added.

In series one there was seventy-six reactions, each metal carbonate macrocycle combination was carried out by the four different methods. There were nineteen combinations of metal carbonate to macrocycle; each of these was carried out at room temperature, with and without triethylamine as the main base, and also in refluxing dichloromethane with and without triethylamine. There was no improvement in yield recorded from the seventy six reactions, with the yield of each of the attempts for macrocycles **351** (3.8 %), **352** (2.1 %), **353** (1.8 % at room temperature and 12 % in refluxing dichloromethane), **354** (8.4 %) and **357** (17 %) from **346** (the *bis*-phenol) with triethylamine present being less than those reported in chapter two, (section 2.3, pages 54-57). As in chapter two, the synthesis of **357**, **358**, **361** and **362** from the *bis*-alcohol starting material failed to yield the target product. These results were seen both at room temperature and in refluxing dichloromethane. The NMR data for these compounds matched that reported in chapter two (pages 118-122 and 129) indicating that the products were not bound to the metals. Each of the attempted synthesis in series one without triethylamine were unsuccessful, with greater than 90 % of the

starting material being recovered, the same result was achieved for the reactions at room temperature and in refluxing dichloromethane.

In series two there were eleven metal carbonate to macrocycle combinations attempted. Again each one was carried out using the four varied methods, resulting in forty-four synthesis attempts. In this series there was no attempt made at the synthesis of **361**. For each of the other macrocycles the results were very similar to those obtained from the series one combinations. For each of the attempts with triethylamine the yields were less than the reported values in chapter two and within experimental variation of those obtained from the series one reactions. The synthesis of macrocycles **357**, **358**, **361** and **362** from the *bis*-alcohols failed. The NMR data of the isolated products matched that from chapter two, which suggests that there was no, or minimal, binding of the metal cation to the macrocycles. The reactions without triethylamine did not yield the target macrocycles, as seen in series one, with the *bis*-alcohol and *bis*-phenol starting materials being obtained in greater than 90 % mass recovery.

In series three there were six metal carbonate to macrocycle combinations screened and each one attempted by the four different methods as previously. As in series one and two above, each of the reactions with triethylamine present resulted in yields less than those reported in chapter two and within experimental error of those obtained from the series one. Again the synthesis of macrocycles **357**, **358**, **361** and **362** from the *bis*-alcohols failed. As was detailed previously the NMR data of the isolated products matched that from chapter two, which suggests that there was no, or minimal, binding of the metal cation to the macrocycles. Also the synthesis attempts without triethylamine did not yield the target macrocycles with more than 90 % mass recovery of the *bis*-alcohol and *bis*-phenol starting materials.

From the investigation in this section it can be seen that the attempts to increase yield by templatation using these metal carbonates was unsuccessful. Although this is a preliminary study and it is possible with different salts of these metals (to increase solubility in the organic media and activity as base), different solvents (both for increased temperature and to aide solubility of the metal salts in the organic media) and different concentrations, that metal templatation with metal cations could work. It is also possible that none of these metal cations can act as a template for the macrocyclisation reactions tested and that to use templatation for the synthesis of these macrocycles the use of another metal (not tested here) may be necessary.

4.3 Conclusion:

A selection of the macrocycles and their precursors synthesised in this project were tested for metal extraction ability against a variety of metal picrates. Compounds **359** and **360** did not extract any of the metal picrates above the error in the calibration curves. Each of the other compounds tested showed extraction of several metal picrates on an individual basis.

Although there are many interesting results with percentage extractions above 15 or even 20 %, none of the metal picrates showed selectivity, i.e. extracted only one metal picrate, instead preferential extraction was observed in many cases, with a higher extraction of one metal picrate observed over each of the other metal picrates. The most obvious case of preferential extractions is the extraction of copper(II) over lanthanum(III) and potassium by **352**, in this case copper(II) is extracted almost nine times the percentage of lanthanum(III) and 15 times the percentage of potassium. But this is not a true test of selectivity as each metal picrate is tested for binding individually and to test for selectivity the picrates would have to be in a mixed solution when extracted by the macrocycle/precursor as the presence of one metal may interfere with the formation of the host-guest complex with another metal. Also to fully determine selectivity of the host compounds there has to be a determination of not only extraction of the metal picrate into the organic, but determination of whether the guest metal is a free cation or is chemically bound to the anion, and on top of that how much of the metal picrate is actually bound to the host compound and how much is in the organic solution.

In order to confirm the host-guest complexes were forming rather than the metal picrate salts simply transferring from the aqueous to the organic the extraction studies were repeated with some modifications. These changes were made to drive the formation of the host-guest complex to as high a conversion as possible and then to record an NMR of as many of the host-guest complexes as possible. These tests were carried out on a variety of compounds with a variety of metal picrates. For each compound chosen the test was carried out with multiple picrates which gave either high binding or low/no binding. The combinations which gave high extractions values were chosen so as to maximise the chances of obtaining an NMR of the host-guest complex. Each of the combinations which gave low extraction values, all of which gave readings that have been reported as not successfully determined, were chosen to show that these results (at or around 0 %) were correct, i.e. no extraction hence no

binding occurred, but also that these metal picrates were not degrading the macrocycle/precursor being used as the host. In each of the cases the experiment was successful showing that not only is the host guest being formed, hence extraction occurring, but also the host molecules are stable to the test conditions.

If this project was to be continued the next stage of testing with these metals would be to carry out the separate solution method of electrochemical testing with ion selective electrodes. This would be done using an electrode with a membrane impregnated with the binding agent. This could then be tested for each metal individually, and the difference between the potentials for each metal can be used to calculate the selectivity co-efficient.

Attempts at the synthesis of the macrocycles *via* metal cation templatation were made using the results of the metal binding testing as a guide for metal selection. Each of these attempts failed to increase the yields of the macrocycles, with the yields being less for those with triethylamine acting as a base and the reactions failing to work without triethylamine. This could be for numerous reasons; the most obvious is that it is possible that the metals chosen will not act as templates for the macrocycles attempted. Also this was only a preliminary study with these metals, it is possible with different metal salts, increasing solubility and alkalinity, or different solvents, allowing higher temperatures and more metal into solution, that these metals could work as templates.

If this was to be worked on further the use of higher temperatures and higher concentrations of both metal and acyclic starting material may lend to better results, along with the use of different metals.

Experimental:

General method for the synthesis of picrate salts:

Sodium Picrate salt synthesis:

0.77 g of the picric acid (65 % suspension in water) was dissolved in enough water at 60 ^{o}C with gentle stirring to make a saturated solution. Sodium carbonate was added slowly to the hot solution of picric acid with gentle stirring until the evolution of carbon dioxide has ceased. The solution was gently stirred for a further 10 minutes and then cooled to 0 ^{o}C.

The sodium picrate product was filtered by gravity filtration and washed with ice cold water (30 mL). The wet product was then removed from the filter paper and transferred

to a storage container. Yields of the products could not be recorded as the agreed preparation of the salts stated that the bulk picrate salts were not to be dried.

Remaining Picrate Salt synthesis:

Each of the other picrate salts, magnesium, calcium, zinc, potassium, lithium, barium, caesium, cadmium, cobalt, copper, strontium, lead and lanthanum picrates were carried out by the same method as was used for the synthesis of sodium picrate.

Picrate Extraction Studies:[78]

A sample of each of the picrate salts was dried *in vacuo*. 35 µmol of each dry picrate salt was accurately weighed, on a 10 µg scale. This was used to accurately make up 500 mL of a 7 x 10^{-5} M solution of each picrate in water. 8.75 µmol of each of the products to be tested (**338**-**344**, **346**, **351**-**354**, **357**-**362** and **368**-**372**) were accurately weighed on a 10 µg scale. This was used to accurately make up 0.5 L of a 1.75 x 10^{-5} M solution of each of the products in chloroform. Due to insufficient sample being isolated and also some of the compounds were not isolated until near the end of the project it was not possible to test each of the picrates with each of the products. The following table is a list of these exceptions.

Product	*Metal in picrate*
370, 361, 360	Cd
	Co
	Cu
	Sr
	Pb
	La

Product	*Metal in picrate*
338, 372	Na
	Mg
	Ca
	Zn
	K
	Li
	Ba
	Cs

Table 49: List of product: metal picrate combinations that were not tested.

Calibration curves of each picrate were made in the range of 7 x 10^{-5} M to 4.6 x 10^{-5} M. The absorbance of each solution was measured at 356 nm on a Varian CARY 50 Scan UV-Visible Spectrophotometer and a calibration curve drawn for each picrate.

6 mL of each picrate solution was mixed with 6 mL of each of the product solutions. All mixtures were shaken on an automatic shaker for ten minutes at 600 oscillations per minute. The mixtures were allowed to settle for ten minutes and separated. Absorbance readings of the aqueous layer were taken at 356 nm. All extractions were

done in triplicate and their UV absorbance readings averaged for the calculations. The mean absorbance was then compared to the calibration curve for each picrate and the percentage extraction calculated. Percentage extraction was determined by calculating the number of moles of metal picrate that transferred to the organic phase and dividing by the number of moles of the binding agent (macrocycle or open structure) in the organic layer, as shown in the formula below.

$$\%\ Extraction = 100\left\{\frac{(M\ Picrate)_o - (M\ Picrate)_e}{(Binding\ Agent)_{org}}\right\}$$

where $(M\ Picrate)_o$ is the number of moles of metal picrate in the aqueous layer originally, $(M\ Picrate)_e$ is the number of moles in the aqueous layer after extraction and $(Binding\ agent)_{org}$ is the number of moles of binding agent in the organic layer.

Blank tests were carried out by extracting a solution of each of the binding agents in chloroform with water and also by extracting an aqueous solution of each of the picrate salts with chloroform.

Picrate Extraction NMR Studies:

Water was added to a sample of cadmium, caesium, cobalt, copper, lanthanum, lead, lithium, magnesium, potassium, sodium and strontium picrate salts to make saturated solutions of each of the picrates. 0.9 mmoles of each of the products to be tested (**338**, **341**, **343**, **351**, **362**, **368** and **369**) was accurately weighed, on a 10 µg scale. This was used to accurately make up 60 mL of a 15 mM solution of each of the products in chloroform.

6 mL of the appropriate picrate solution was mixed with 6 mL of the appropriate product solutions, detailed in table 50 below. All mixtures were shaken on an automatic shaker for ten minutes at 600 oscillations per minute. The mixture were allowed to settle for ten minutes and then separated.

Macrocycle/Precursor	Metal Picrate
338	Cd, Sr, Cu
341	Cu, Mg, Cs, Sr
343	La, Li, Co, Cs, Na
351	Cu, Cd, Li, Na, Co, Sr
362	Cu, Cd, Cs, Co, Mg, Na
368	Cu, Mg, Cs, K, Na
369	Co, Co, Pb, La

Table 50: Combinations of Macrocycles/Precursors with metal picrates

The chloroform was removed under vacuum and the solid was dissolved in 1.5 mL deuterated chloroform and then its proton NMR was recorded, and in some cases its carbon NMR was also recorded. For the comparison NMR spectra; 6 mL of each product solution, in chloroform, had the solvent removed *in vacuo*; were then dissolved in deuterated chloroform and had their NMR spectra were recorded in triplicate. Each of the products should have been approximately 60 mM in the deuterated chloroform. 20 mM and 40 mM solutions in deuterated chloroform were made by dilution of the 60 mM solution in deuterated chloroform. Their NMR spectra were also recorded at 20 mM and 40 mM in triplicate.

The NMR spectra of the hosts before and after extraction with the metal picrates were then compared to ascertain if the host-guest complex had formed.

General method for the synthesis of macrocycles using metal templatation at room temperature without triethylamine:

The appropriate *bis*-alcohol or *bis*-phenol (2.4 mmol) was dissolved in dry dichloromethane (5.0 mL) at room temperature under nitrogen. Dry metal carbonate (14.4 mmol) was added. The appropriate dichloride (2.4 mmol) was dissolved in dry dichloromethane (15.0 mL) and added slowly to the reaction mixture. The reaction mixture was then left stirring for 16 hour at room temperature. After this time had elapsed the reaction was quenched by adding distilled water (10.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X3), saturated ammonium chloride solution (50.0 mL) and saturated sodium chloride solution (50.0 mL). The organic layer was dried over

magnesium sulphate and the solvent was removed *in vacuo* yielding the crude product. The products were purified by the same method as reported in the experimental section of chapter two, pages 118-122 and 129.

General method for the synthesis of macrocycles using metal templatation in refluxing dichloromethane without triethylamine:

The appropriate *bis*-alcohol or *bis*-phenol (2.4 mmol) was dissolved in dry dichloromethane (5.0 mL) at room temperature under nitrogen. Dry metal carbonate (14.4 mmol) was added. The solution was then heated to reflux. The appropriate dichloride (2.4 mmol) was dissolved in dry dichloromethane (15.0 mL) and added slowly to the reaction mixture. The reaction mixture was left stirring for 16 hour at reflux. After this time had elapsed the reaction was allowed to cool to room temperature and quenched by the addition of distilled water (10.0 mL) and stirred for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X3), saturated ammonium chloride solution (50.0 mL) and saturated sodium chloride solution (50.0 mL). The organic layer was dried over magnesium sulphate and the solvent was removed *in vacuo* to leave behind the crude product. The products were purified by the same method as reported in the experimental section of chapter two, pages 118-122 and 129.

General method for the synthesis of macrocycles using metal templatation at room temperature with triethylamine:

The appropriate *bis*-alcohol or *bis*-phenol (2.4 mmol) was dissolved in dry dichloromethane (5.0 mL) at room temperature under nitrogen. Dry metal carbonate (14.4 mmol) and dry triethylamine (5.8 mmol) were added. The appropriate dichloride (2.4 mmol) was dissolved in dry dichloromethane (15.0 mL) and added slowly to the reaction mixture. The reaction mixture was left stirring for 16 hour at room temperature. After this time had elapsed the reaction was quenched by adding distilled water (10.0 mL) and stirred for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X3), saturated ammonium chloride solution (50.0 mL) and saturated sodium chloride solution (50.0 mL). The organic layer was

dried over magnesium sulphate and the solvent was removed *in vacuo* to yield the crude product. The products were purified by the same method as reported in the experimental section of chapter two, pages 118-122 and 129.

General method for the synthesis of macrocycles using metal templatation in refluxing dichloromethane with triethylamine:

The appropriate *bis*-alcohol or *bis*-phenol (2.4 mmol) was dissolved in dry dichloromethane (5.0 mL) at room temperature under nitrogen. Dry metal carbonate (14.4 mmol) and dry triethylamine (5.8 mmol) were added. The solution was heated to reflux. The appropriate dichloride (2.4 mmol) was dissolved in dry dichloromethane (15.0 mL) and added slowly to the reaction mixture. The reaction mixture was left stirring for 16 hour at reflux. After this time had elapsed the reaction was allowed to cool to room temperature and quenched by adding distilled water (10.0 mL) and stirring for ten minutes. The reaction mixture was transferred to a separation funnel and the organic and aqueous layers were separated. The organic layer was washed with distilled water (50.0 mL X3), saturated ammonium chloride solution (50.0 mL) and saturated sodium chloride solution (50.0 mL). The organic layer was then dried over magnesium sulphate and the solvent was removed *in vacuo* yielding the crude product. The products were purified by the same method as reported in the experimental section of chapter two, pages 118-122 and 129.

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Chapter 5:

Biological screening of selected products successfully isolated in this project.

5.1 Introduction:

Crown ethers have been developed which show potent inhibition of cell proliferation and new systems are being exploited to kill microbial organisms.[79] Functionalized crowns have also been synthesized to bind and cleave DNA and have led to investigative drug studies in cancer research. Also some natural crown ethers, such as Nonactin **1**, are antimicrobial agents. As it has been shown that crown ethers act as antimicrobial agents by a variety of methods it was decided to test a sample of the water soluble macrocycles synthesised in this project for their antibacterial properties. This investigation was carried out prior to the metal binding in chapter four as a preliminary screening and therefore it was unknown at that stage if the macrocycles bind to any biologically active metal cations.

There is a large diversity of structures of known p-gp inhibitors; with examples ranging from polyethylene glycol to more rigid structures e.g. progesterone. Some macrocycles have been shown to be P-gp inhibitors e.g. **270** and **271** (chapter 1).[55, 57, 58] The P-gp inhibitors can act in a number of ways, from being high-affinity substrates of the pump; efficient inhibitors of ATP hydrolysis coupled P-gp transport and; partial substrates/inhibitors. High-affinity substrates of the pump will be expelled from the cell at a high rate and this will reduce the rate at which P-gp can remove other compounds from the cell. Efficient inhibitors of ATP hydrolysis coupled P-gp transport decrease the rate of ATP hydrolysis, therefore P-gp will not obtain the energy required to pump it's substrates from the cell. Partial substrates/inhibitors bind to P-gp but P-gp cannot pump these molecules out of the cell and so P-gp is inhibited from eliminating other compounds from the cell. With the knowledge that some macrocycles have been shown to inhibit P-gp, and the fact that there are multiple ways in which P-gp inhibition can occur, it was decided to test each of the water soluble macrocycles for P-gp inhibition.

5.2 Results:

5.2.1 Antibacterial testing

343, **344**, **346**, **351-353**, **357-359** and **362** (figure 119) were tested for minimum inhibitory concentration against *Pseudomonas aeruginosa, Escherichia coli, Klebsiella spp., Staphylococcus aureus, Salmonella spp., Enterococcus spp.* and *Bacillus subtilis* over the concentration range 0-2000 µg/mL.

Minimum inhibitory concentrations (MICs) for the compounds were determined by serial two-fold dilutions in Mueller-Hinton broth using the broth micro-dilution method described by Amsterdam.[80]

The bacterial strains were grown in Mueller-Hinton broth overnight. The compound to be tested was dissolved in sterile water and diluted in the test medium to twice the top concentration desired in the test, i.e., the highest desired concentration was 2000 µg/mL, so the compound to be tested was diluted to 4000 µg/mL. Ten serial two-fold dilutions of the compound to be tested were made. Into each of the diluted solutions was added a sample of the bacteria to be tested. The plates were then incubated and checked after 18 and 36 hours, with the MIC being reported as the lowest concentration of the compound that completely inhibited growth of the organism as detected by the unaided eye.

Compounds that were water-insoluble were diluted in methanol. The MICs for these compounds were obtained using the same procedure described above. However, instead of diluting the compound directly in Mueller-Hinton broth, 20 µL of the solution (to give a final concentration of 2000 µg/mL) was added to the first well in the row. The methanol was allowed to evaporate and then 200 µL of Mueller-Hinton broth was added, mixed and diluted using serial two-fold dilutions as described above.

All tested compounds showed no activity at the tested concentration range, with MIC values >2000 µg/mL.

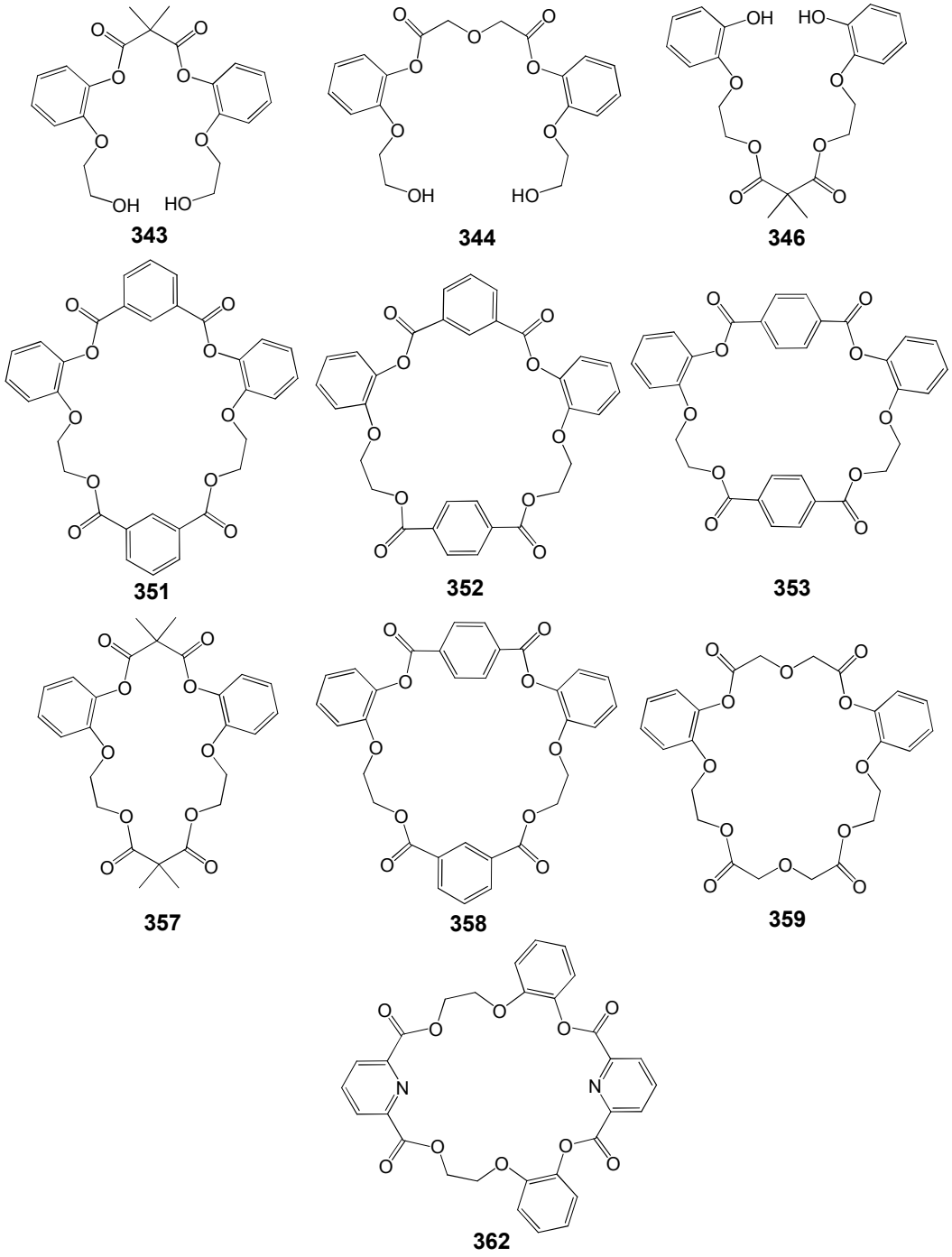
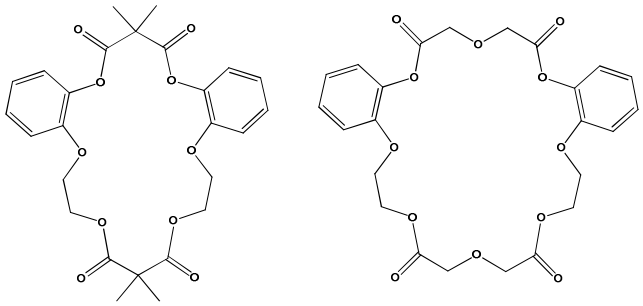


Figure 119: Compounds tested for their antibacterial properties.

At the same time these compounds were tested for antibacterial activity a number of samples were undergoing testing as P-gp inhibitors. Initial results from the P-gp inhibition testing gave positive results so no more work was undertaken examining and developing antibacterial properties.

5.2.2 P-gp inhibition testing

The first two compounds that were examined for inhibition of P-gp were **357** and **359**, structures shown in figure 121.

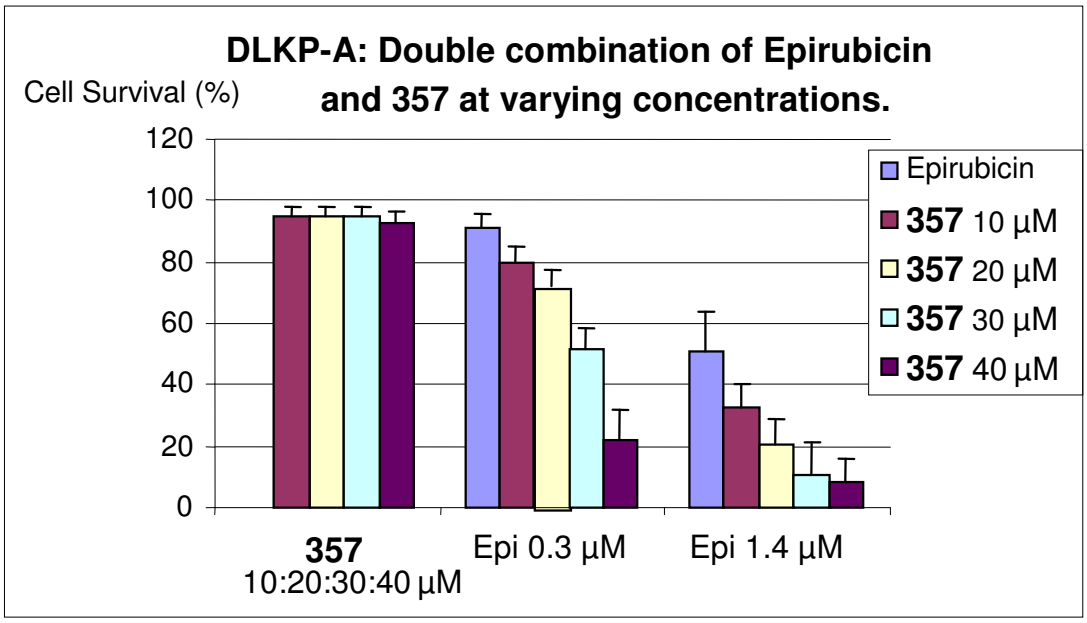


357 359

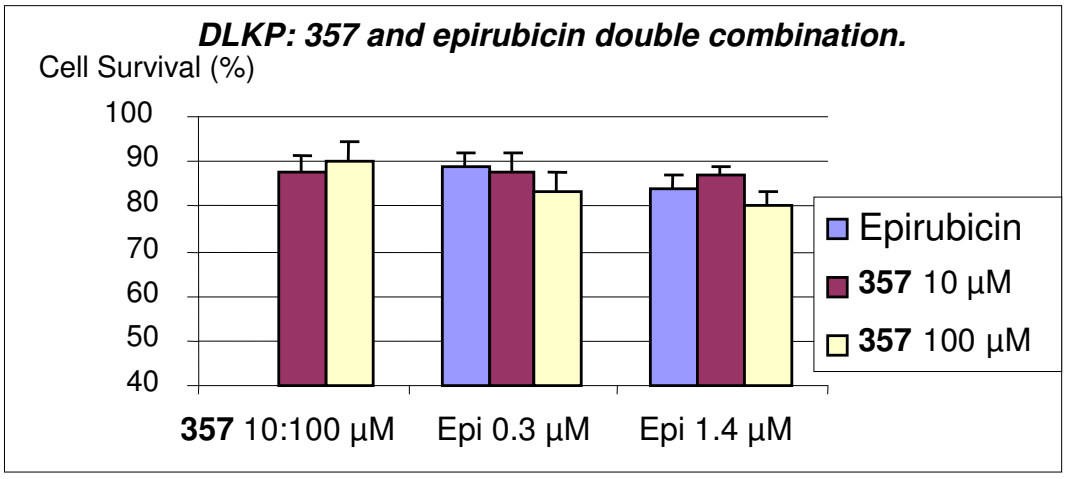
Figure 121: Structures of **357** and **359**

The compounds were studied for their anti-proliferative effectiveness against DLKP and DLKP-A cell lines, alone and in combination with the widely used chemotherapeutic drug Epirubicin. The DLKP cell line is a poorly differentiated squamous cell lung carcinoma. The main mechanism of MDR for DLKP is *via* multidrug resistance associated protein 1 (MRP1) while it poorly expresses P-gp. DLKP-A cell line is a daughter cell line of DLKP and highly expresses P-gp while expressing very low levels of MRP1.

Epirubicin was shown to have an IC_{50} of 0.017 ±0.0008 µM on the DLKP cell line and 2.1 µM ±0.24 on the DLKP-A cell line. Initial testing of **357** at concentrations of 40 µM with Epirubicin (0.3 µM) a significant increase in cell kill occurred in DLKP-A, a 5-fold increase as seen in graph 1 below. Under the same conditions but with DLKP no significant increase occurred, as shown in graph 2.

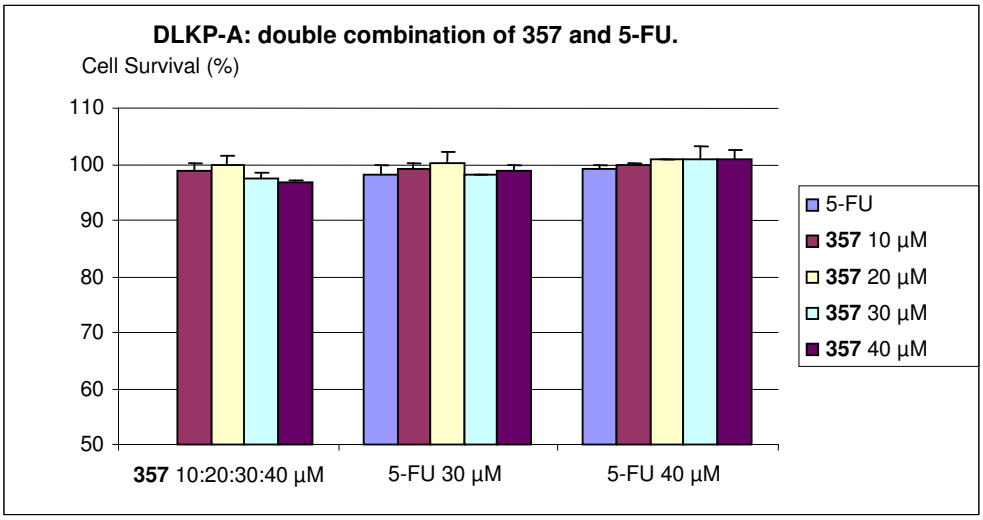


Graph 1: Double combination of **357** *with epirubicin on the DLKP-A cell line.*

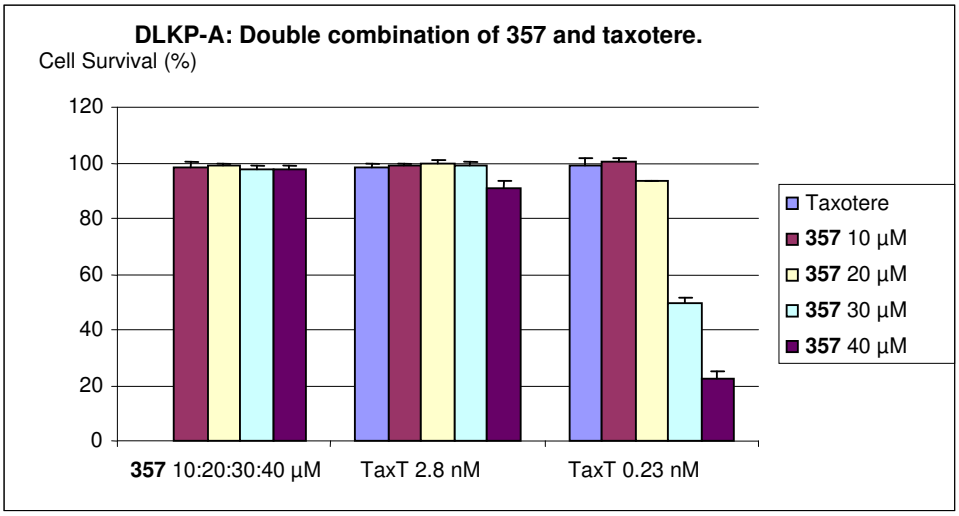


Graph 2: Double combination of **357** *with epirubicin on the DLKP cell line.*

At this concentration of Epirubicin (0.3 µM) without **357** the survival of cell line DLKP-A was not significantly affected, i.e. the cell kill from Epirubicin was close to zero. Also **357** in the absence of Epirubicin had no significant effect on cell survival. **357** was further examined with 5-flourouracil (5-FU) and taxotere on the DLKP-A cell line. The IC_{50} values of 5-FU and taxotere on the DLKP-A cell line are 59 ±1.9 µM and 87 ±6.7 nM respectively. 5-FU is not affected by P-gp and as such no improvement in cell kill occurred when **357** was added as shown in graph 3. Taxotere is pumped from the cell by P-gp and at a concentration of 0.23 nM taxotere and 30 µM **357** an improved cell kill was recorded as shown in graph 4.

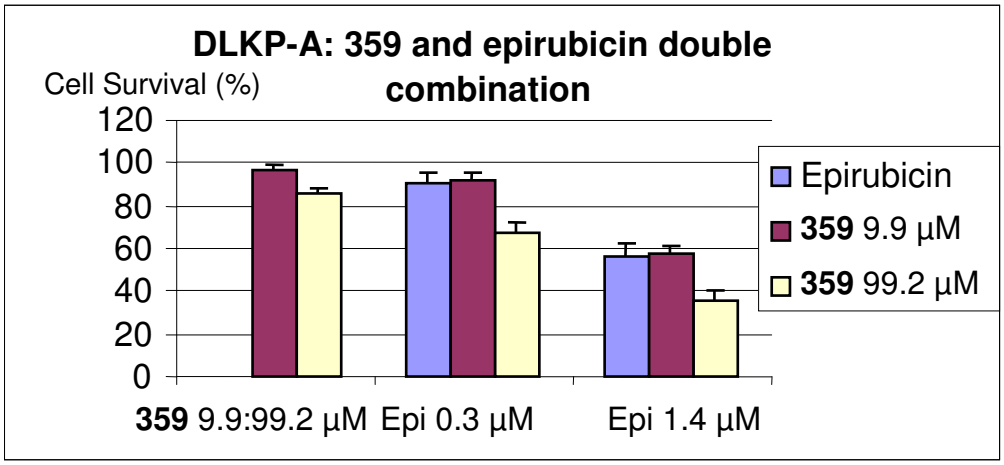


Graph 3: Double combination of **357** *with 5-FU on the DLKP-A cell line.*



Graph 4: Double combination of **357** *with taxotere on the DLKP-A cell line.*

Initial testing on **359** also indicated that this compound lead to decreased cell survival when used in combination with epirubicin as seen in graph 5.



Graph 5: Double combination of **359** *with epirubicin on the DLKP-A cell line.*

As the apparent activity of **359** was not as pronounced as that of **357** it was decided, in consultation with the biologists, who carried out the testing, not to pursue this product for its potential as a P-gp inhibitor. Instead it was decided to focus on the potential decomposition products of **357**. Macrocycle **357** could decompose both in the media and in the cell. The decomposition of **357** in the aqueous biological media would most likely be caused by the hydrolysis of the ester bonds and may be catalysed by the buffers in the media. If it is in the cell that the decomposition takes place the ester bonds could hydrolyse chemically within the cell or in an enzymatic reaction by an esterase or hydrolase enzyme.

On analysis of the structure of **357** it was concluded there were four most probable decomposition products of **357** with further decomposition products possible such as *ortho*-catechol by breaking the ether bond in 2-(2-hydroxyethoxy)phenol. The four decomposition products deemed most feasible were **343**, **346**, 2-(2-hydroxyethoxy)phenol and dimethylmalonic acid (figure 122). This was concluded because the ester bonds in **357** are susceptible to hydrolysis and the likely products of the hydrolysis of the ester bonds are **343**, **346** and the starting materials for the synthesis of **357**.

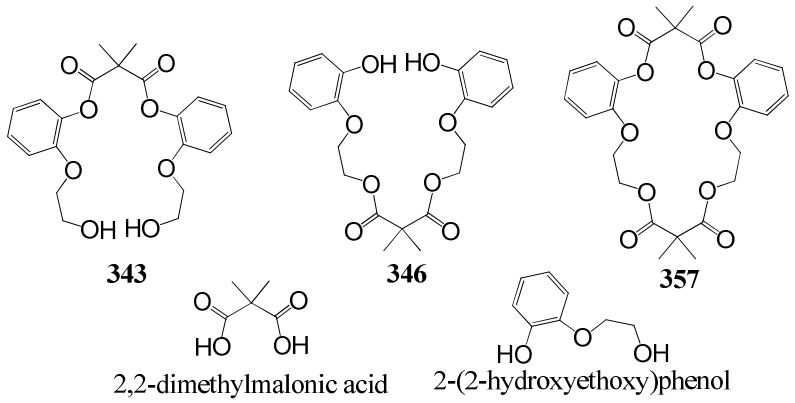


Figure 122: Structures of **357** *and its most probable decomposition products.*

For the next round of testing 2-(2-hydroxyethoxy)phenol (**336**), dimethylmalonic acid, 2,2'-(2,2'-(propane-1,3-diyl*bis*(oxy))*bis*(2,1-phenylene))*bis*(oxy)diethanol (**399**), 2,2'-(2,2'-(2,2'-(ethane-1,2-diyl*bis*(oxy))*bis*(ethane-2,1-diyl))*bis*(oxy)*bis*(2,1-phenylene))-*bis*(oxy)diethanol (**400**), 2,2'-(2,2'-(1,2-phenylene*bis*(methylene))*bis*(oxy)*bis*(2,1-phenylene))*bis*(oxy)diethanol (**401**), 2,2'-(2,2'-(1,3-phenylene*bis*(methylene))*bis*(oxy)-*bis*(ethane-2,1-diyl))*bis*(oxy)diphenol (**402**) and **343** were submitted. Products **399**-**402** (figure 123) were synthesised by another member of the group and any further

testing and results on these compounds are contained in their work.[84] **399**-**402** were included in the testing in an effort towards the identification of the pharmocophore.

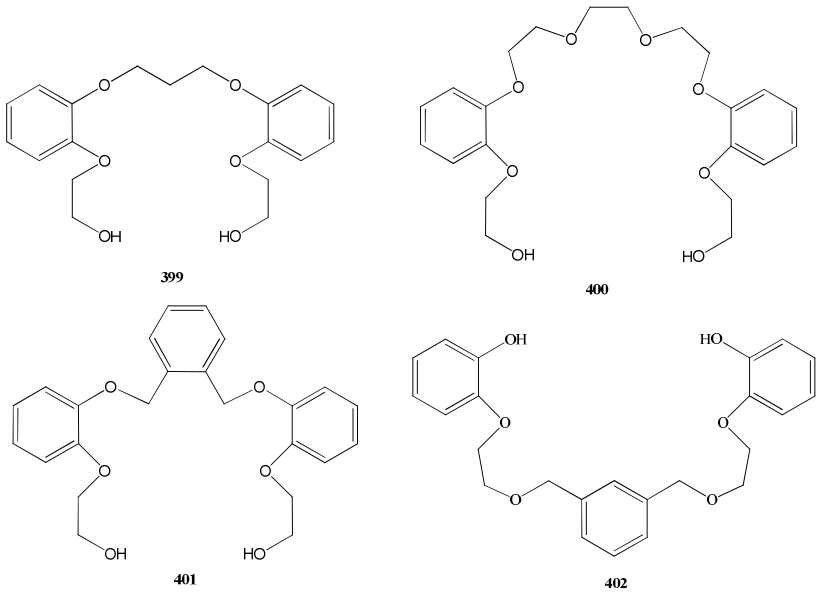
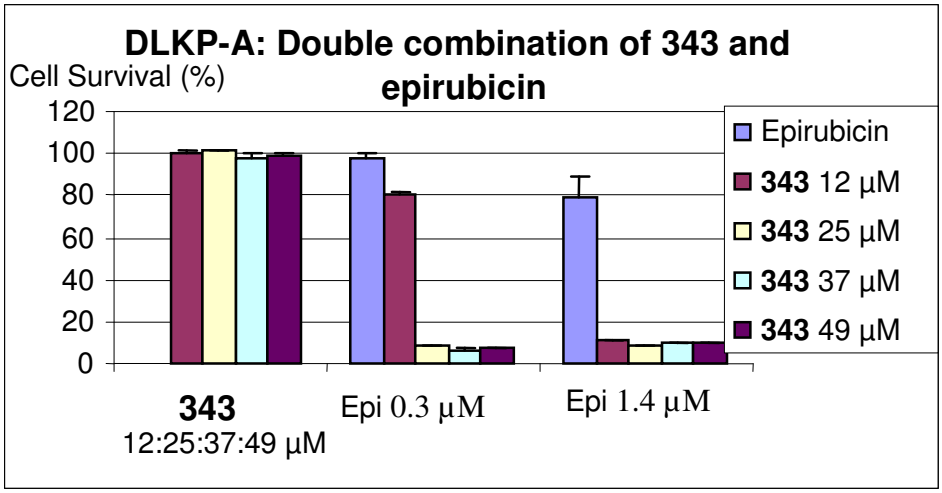


Figure 123: Structures of **399-402**.

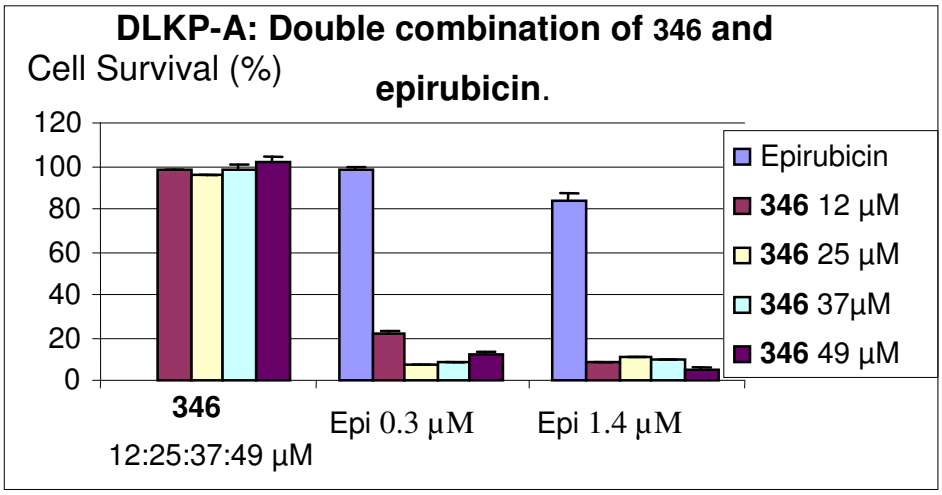
346 at this stage had not been synthesised and its synthesis was carried out and then the product was submitted for testing. The results from this round of testing indicated that **336** and dimethylmalonic acid showed no inhibition of P-gp. The results, graphs 6 and 7, also show that both **343** and **346** had a significant effect on cell survival in conjunction with epirubicin. This indicates that **343** and **346** are effective P-gp inhibitors. The results, shown in graph 8, indicate that **399** also inhibits P-gp but less effectively than **357**, **343** and **346**.

The testing showed that **343** at a concentration of 25 μM with Epirubicin (0.3 μM) a significant decrease in cell survival occurred in DLKP-A, a 10-fold decrease as seen in graph 6. When the epirubicin concentration is increased to 1.4 μM the lower concentration of 12 μM **343** is sufficient to achieve the same cell survival rate.



Graph 6: Double combination of **343** *with epirubicin on the DLKP-A cell line.*

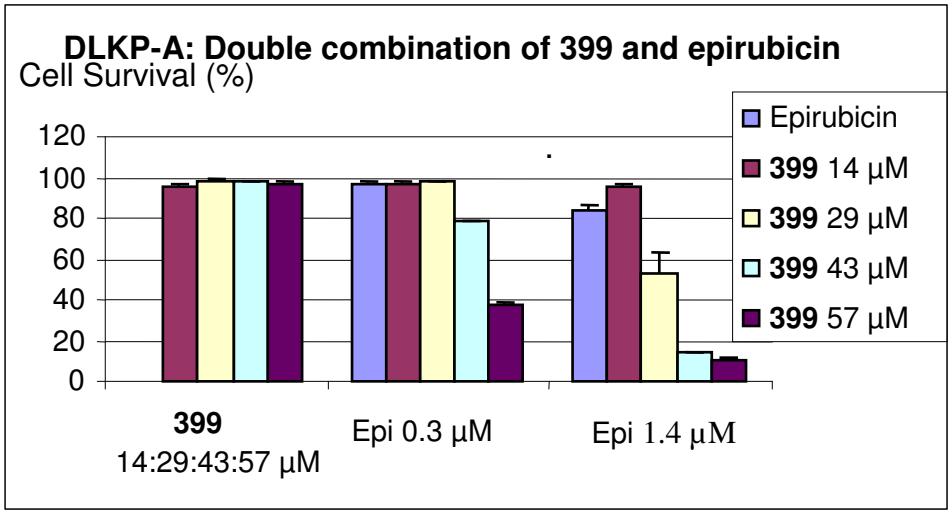
The testing of **346** at concentrations of 12 µM with Epirubicin (0.3 µM) showed a significant increase in cell kill occurred in DLKP-A, with only 20 % cell survival as seen in graph 7, and **346** at concentrations of 25 µM with Epirubicin (0.3 µM) a further decrease in cell survival occurs, with less than 10 % of the cells surviving.



Graph 7: Double combination of **346** *with epirubicin on the DLKP-A cell line.*

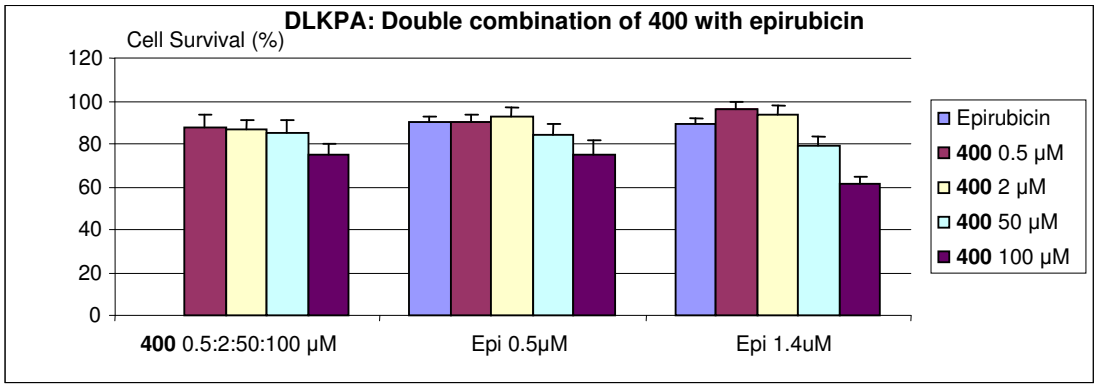
343 and **346** had similar activity except with concentrations of epirubicin (0.3 µM) and 12 µM of the compound being tested. At these concentrations cell survival for **346** was approximately 20 % but using **343** was approximately 80 %. For each of the other concentrations of **343** and **346** with epirubicin at 0.3 µM the cell survival levels were comparable. With epirubicin at the more concentrated 1.4 µM the cell survival were similar for concentrations 12, 25 and 27 µM of **343** and **346**, but at the 49 µM of **346** the cell survival was approximately half of the cell survival with **343** at the same concentration.

The testing showed that **399** at concentrations of 57 µM with 0.3 µM Epirubicin a significant increase in cell kill occurred in DLKP-A, with only 40 % cell survival as seen in graph 8 below, and **399** at concentrations of 43 µM with 1.4 µM Epirubicin a further decrease in cell survival occurs, with only 15 % now surviving.



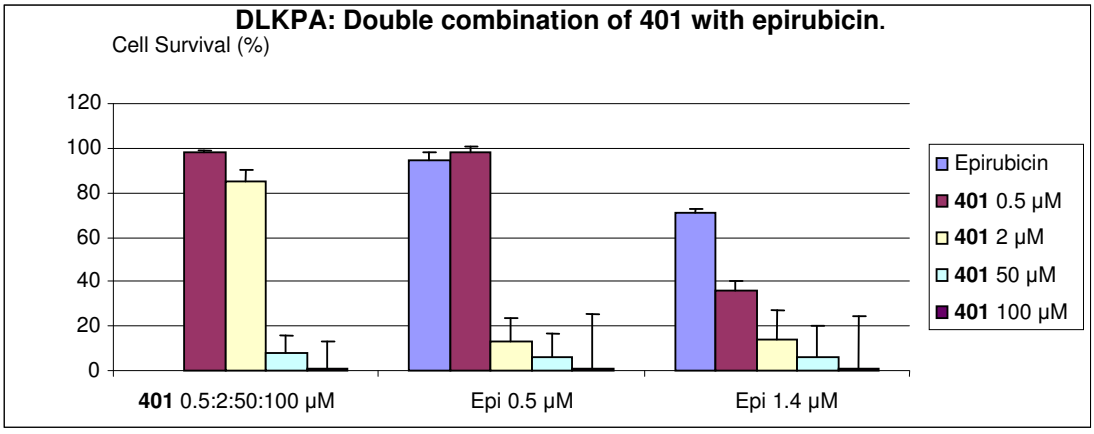
Graph 8: Double combination of **399** *with epirubicin on the DLKP-A cell line*

Compound **400** did not show any synergy with epirubicin, thus suggesting it did not inhibit P-gp (graph 9).



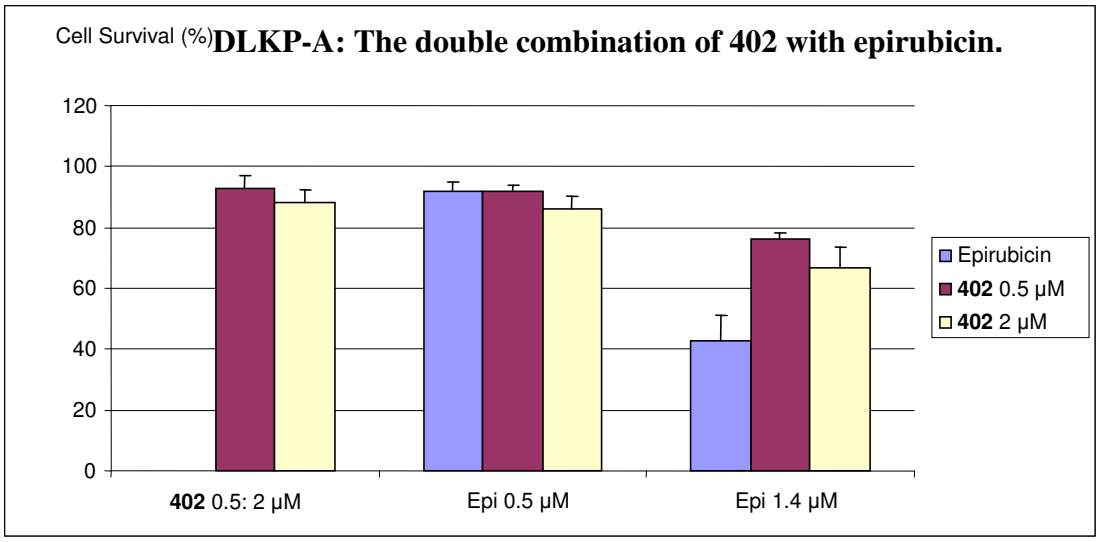
Graph 9: Double combination of **400** *with epirubicin on the DLKP-A cell line.*

In graph 10 the synergistic effect was observed with **401** at a concentration of 2µM and epirubicin at 0.5µM. With a lower concentration of **401**, 0.5µM, and a slightly higher concentration of epirubicin, 1.4µM, synergy was also observed.



Graph 10: Double combination of **401** *with epirubicin on the DLKP-A cell line.*

Graph 11 below shows the effects of **402** on the DLKP-A cell line when used in combination with epirubicin. It was seen to have a slight antagonistic effect at the higher concentration of epirubicin with both concentrations of **402** that were tested on the DLKP-A cell line.



Graph 11: Double combination of **349** *with epirubicin on the DLKP-A cell line.*

At this stage in the development of a P-gp inhibitor three lead compounds had been identified, **343**, **346** and **401**. It was decided to concentrate efforts on the optimisation of the synthesis of **346**, the most promising lead compound of this project. The reason for this was to produce sufficient material for full analysis of the compound as a P-gp inhibitor. Optimisation would also lead to a high throughput synthesis to isolate more material for any further testing which may be deemed necessary depending on the outcome of the P-gp inhibition testing. The optimisation process is outlined in chapter 2, page 68.

When samples from the optimised method of synthesis were submitted for continued testing issues arose with the solubility of **346**. The product would not dissolve at the same concentrations in the same media as was previously possible. Previously 10 mg of **346** had been dissolved in 1.0 mL ethanol and then added to the aqueous media for biological testing. However the product of the optimised synthesis of **346** would not dissolve at same concentration 10 mg/mL in ethanol. From the evidence available, NMR (carbon and proton), MP, R_f and IR, the product could not be differentiated from that which was originally synthesised. This shows that the structure of the product is the same as that originally generated. The evidence thus indicates that the issue arose either due to a low level impurity in the originally synthesised **346** which aided solubility or to a low level impurity in **346** from the optimised synthesis which hindered solubility. The possibility of different crystal structures of the product could also explain different solubilities of the compound in solution as different crystal matrices can have different solubilities in varying solvents.[81] Ordinarily different crystal structures would lead to different melting points, however this possibility cannot be ruled out. Also different crystal forms can lead to different biological activity[82] due to the different shape of the molecule in the crystal and this varied shape can then interact differently with the target species.

A thorough investigation of **346** and its synthesis was then undertaken as a priority. This study started by synthesising **346** multiple times using the original method developed, each time changing the work up of the product at each step in an attempt to isolate **346** that had comparable solubility to the original batch of **346**. The original batch of **346** was soluble in ethanol at 10 mg/mL and remained in solution when added to the biological media. The work in this project was carried out in two laboratories in two separate buildings. The initial synthesis of **346** was carried out in laboratory X249 in the School of Chemical Sciences, but due to the relocation of the research group to the National Institute of Cellular Biotechnology building all the other syntheses were carried out in laboratory G23. In the different laboratories the DI water came from different sources, in X249 the DI water is obtained from a Millipore system and in G23 there is a building wide DI water system. So when this work was undertaken it was important to use the water from X249 in some of the attempts. Table 51 outlines the attempts made.

Work up of TES protection stage	**Work up of synthesis of triethylsilyl protected *bis*(2-(2-hydroxyphenoxy)ethyl) 2,2-dimethylmalonate**	**Work up of deprotection step**
Original work up: quenched with H_2O, Washed with water and then saturated NH_4Cl, Dried over $MgSO_4$, Column chromatography for purification	Original work up: quench with H_20, wash with water, dry over $MgSO_4$, Column chromatography	Original work up: quenched with Na_2CO_3, washed with water and then saturated $NaHCO_3$, dried over $MgSO_4$, Chromatography and recrystallisation for purification
Same as original but also an added NaCl wash	Same as original but with added an added NaCl wash	Same as original but quenched with K_2CO_3
Same as original but NaCl wash instead of NH_4Cl wash	Same as original but with added NaCl and NH_4Cl wash	Same as original but quenched with triethylamine
Same as original but with added KCl wash	Same as original but with an added KCl wash	Same as original but quenched with sodium hydroxide
Same as original but also an added KCl wash and NaCl wash	Same as original but also an added KCl wash and NaCl wash	Same as original but quenched with potassium hydroxide
Same as original but with KCl wash and NaCl wash instead of NH_4Cl	Same as original but with KCl wash and NaCl wash and NH_4Cl	Same as original but with KCl wash and NaCl wash and NH_4Cl wash
Same as each above but dried over Na_2SO_4	Same as original but with added NH_4Cl wash	Same as original but with added KCl wash
Same as each above but using tap water instead of DI water	Same as original but with KCl wash and NH_4Cl was	Same as original but with added KCl wash and NaCl wash
Same as each above but using water from X249 instead of water G23	Same as each above but using water from X249 instead of water G23	Same as original but with NH_4Cl wash
		Same as original but with added NaCl wash
	Same as each above but using tap water instead of DI water	Same as original but with NaCl wash and NH_4Cl wash
	Same as each above but dried over Na_2SO_4	Same as original but with KCl wash and NH_4Cl wash
		Same as each above but dried over Na_2SO_4
		Same as each above but using tap water instead of DI water
		Same as each above but using water from X249 instead of water G23

Table 51: Attempts at working up **346** *to make soluble in the biological media*

Each of the work-ups in table 51 were carried out in conjunction with each of the work-ups from the other columns. So for example from column "work up of TES protection stage" the original work-up was split into nine samples, one sample for each of the work-ups in the "work-up of synthesis of triethylsilyl protected *bis*(2-(2-hydroxyphenoxy)ethyl) 2,2-dimethylmalonate" column, then each sample from this was split into fifteen samples to be worked up by each method in the "work up of deprotection step" column. This gave one thousand, four hundred and eighty five samples each of which were tested for solubility in ethanol at 10 mg/mL. A sample of each solution in ethanol was added to biological media to test if the **346** would stay in solution in the media. All of the attempts to synthesise **346** again with different work-ups failed to give a sample which would stay in solution when added to the media.

The next step was an attempt to make a solution of **346** at the required concentration, 10 mg/mL, in such a way that **346** would stay in solution when added to the biological media. This was examined both directly using heat and sonication and indirectly by making a solution in an organic solvent (e.g. ethanol) then mixing this solution with the media. Table 52 below shows the attempts to solublise **346** in the biological media.

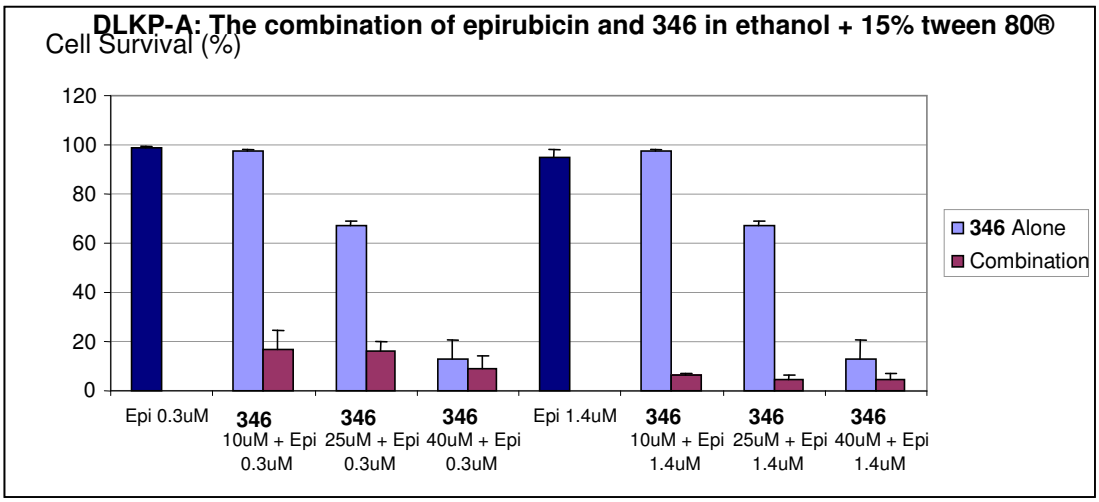
Solvent (mixture)	Additive	Successful (yes or no)
Ethanol	none	no
Ethanol : water [a]	none	no
DMSO	none	no
DMSO : water [a]	none	no
DMSO : Ethanol [a]	none	no
DMSO : Ethanol : water [a]	none	no
Ethanol	NaCl, KCl, NH_4Cl [b]	no
Ethanol : water [a]	NaCl, KCl, NH_4Cl [b]	no
DMSO	NaCl, KCl, NH_4Cl [b]	no
DMSO : water [a]	NaCl, KCl, NH_4Cl [b]	no
DMSO : Ethanol [a]	NaCl, KCl, NH_4Cl [b]	no
DMSO : Ethanol : water [a]	NaCl, KCl, NH_4Cl [b]	no
Ethanol	Cremophor EL®, NaCl, KCl, NH_4Cl [b]	no
Ethanol : water [a]	Cremophor EL®, NaCl, KCl, NH_4Cl [b]	no
DMSO	Cremophor EL®, NaCl, KCl, NH_4Cl [b]	no
DMSO : water [a]	Cremophor EL®, NaCl, KCl, NH_4Cl [b]	no
DMSO : Ethanol [a]	Cremophor EL®, NaCl, KCl, NH_4Cl [b]	no
DMSO : Ethanol : water [a]	Cremophor EL®, NaCl, KCl, NH_4Cl [b]	no
Ethanol	Tween 80®, NaCl, KCl, NH_4Cl [b]	yes, 15 % tween 80® in ethanol dissolved **346** and also it stayed in solution for biological screening. [c]
Ethanol : water [a]	Tween 80®, NaCl, KCl, NH_4Cl [b]	no
DMSO	Tween 80®, NaCl, KCl, NH_4Cl [b]	no
DMSO : water [a]	Tween 80®, NaCl, KCl, NH_4Cl [b]	no
DMSO : Ethanol [a]	Tween 80®, NaCl, KCl, NH_4Cl [b]	no
DMSO : Ethanol : water [a]	Tween 80®, NaCl, KCl, NH_4Cl [b]	no

Table 52: Attempts at solublising **346** *in the biological media.*

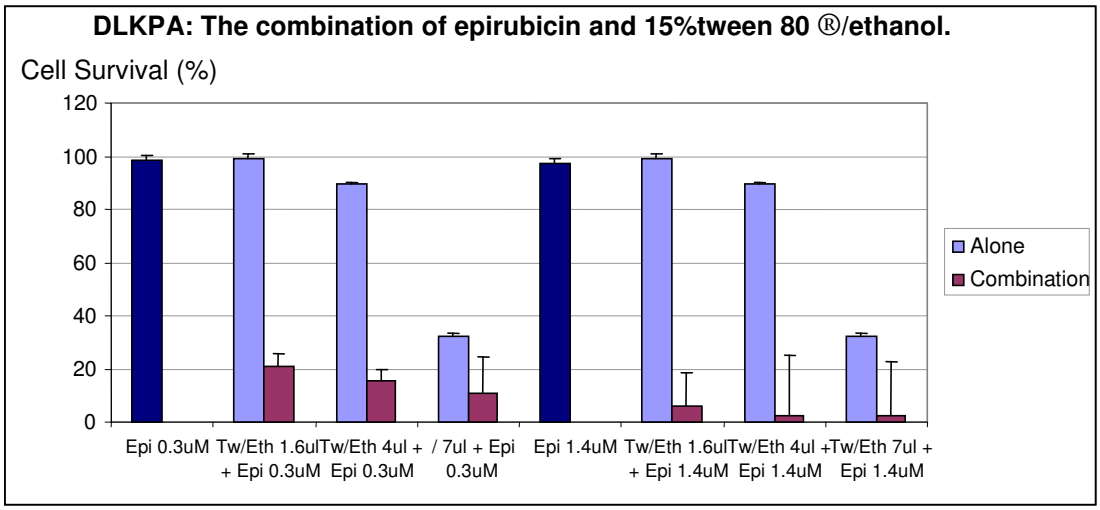
[a]: various different ratios of these solvents were used. [b]: each of these additives were used individually and in conjunction with each other. [c]: also worked at higher concentrations of tween 80® but lower concentrations of additives lead to less complications in the biological screening.

Each mixture was heated and sonicated as necessary to dissolve **346**. No sonication or heating above 35 ^{o}C was allowed when added to the biological media, as this could not

be done when the P-gp inhibition testing was preformed. In table 52 "successful" means that a solution was made which when added to the biological media no solid crashed out of solution. A sample of **346** was then submitted which was to be dissolved in ethanol with 15 % tween 80®. This sample would then be added to the biological media containing DLKP-A cells. Tween 80® has previously been shown to inhibit P-gp[83] therefore a blank test with the 15 % tween 80® in ethanol without **346** was carried out. The results of these tests are shown in graphs 12 and 13.



Graph 12: **346** *in ethanol with 15 % tween 80®*



Graph 13: 15 % tween 80® in ethanol

The synergistic effect of the solution of **346** in ethanol with 15 % tween 80® could not be distinguished from that of the blank test, as seen in graphs 12 and 13. From these results it was evident that **346** was not giving the same synergistic effect as was seen in the initial synthesis of the product. This indicates that the initial batch of **346** synthesised was different to each of the repeat synthesis. The inconsistency between

the original result and repeat syntheses is currently unknown, the NMR spectra of the products from the original synthesis and that of the optimised show the products to be alike as seen in figures 124 and 125 below. Although in the NMR spectrum of the initial synthesis the peaks are less well defined than those from the optimised synthesis and there are small variations in the chemical shifts this seems to be more likely due to error in the NMR spectrum. Most likely these minor variations arise from temperature variations and/or concentration differences in the samples. Each of the peaks are in the correct location in the spectra with small variations. They are not identical but are not significantly different from each other and they are each significantly different from the NMR spectrum of **343**.

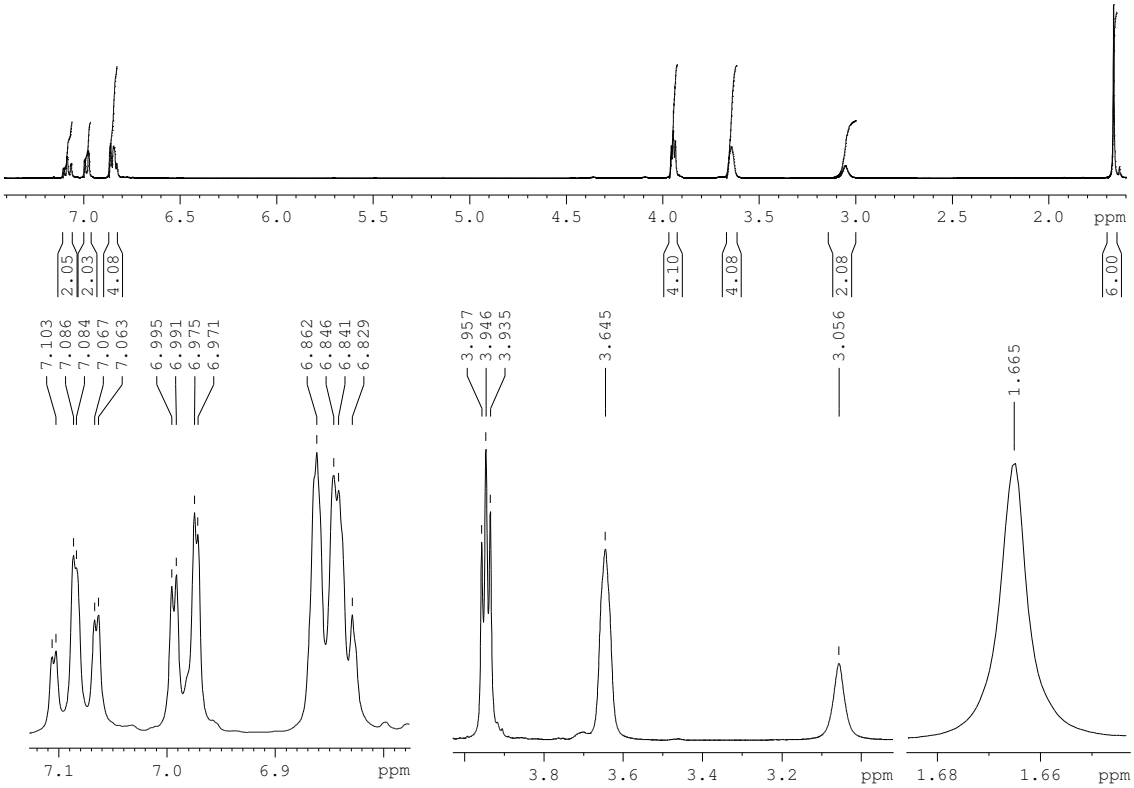


Figure 124: ^{1}H-NMR of **346** *from initial synthesis*

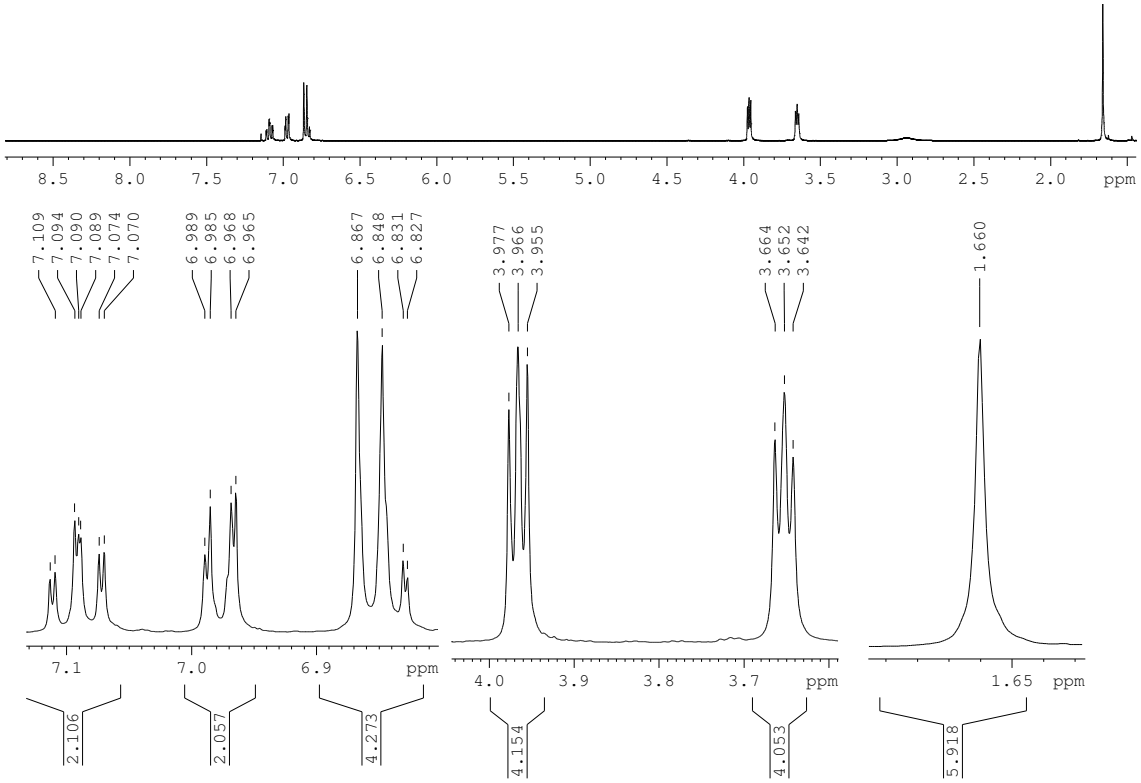
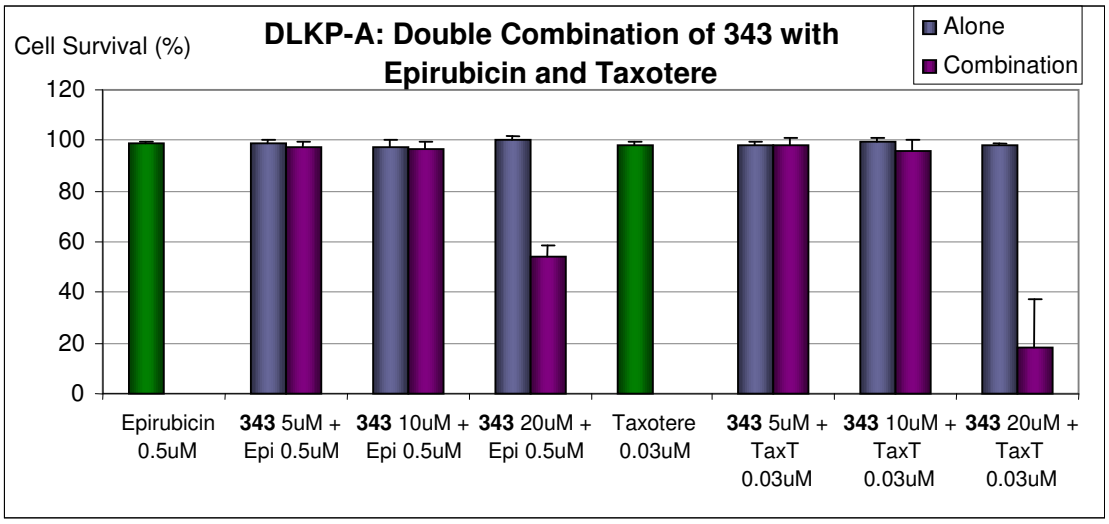


Figure 125: ^{1}H-NMR of **346** *from optimised synthesis*

This meant that the results originally obtained from the P-gp inhibition testing of **346** could not be reproduced, and hence could not be confirmed.

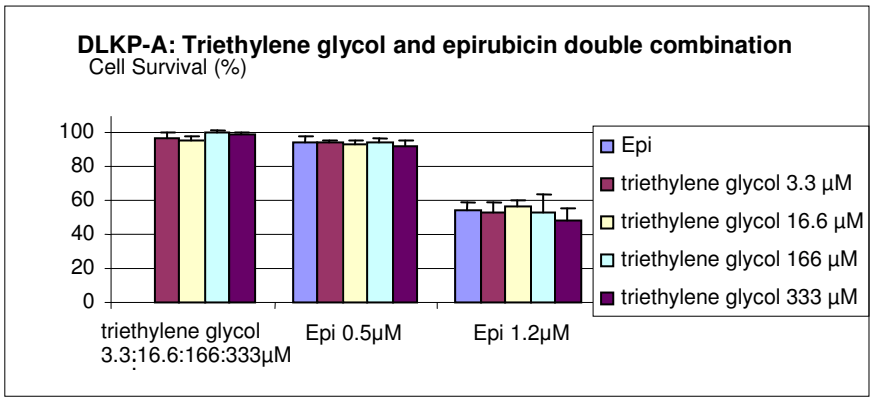
In an effort to confirm that **343** and **346** were not confused with each other on testing a new sample of **343** was synthesised and the P-gp inhibition testing with this new batch was repeated on the DLKP-A cell line. Also the test was carried out in combination with taxotere, which had not been reported previously. The results of this test showed that this new batch of **343**, the same compound as confirmed by X-ray crystallography in chapter 2 (page 80) inhibited P-gp and thus increased the cell kill rate when acting in combination with Epirubicin and in combination with Taxotere (graph 14).



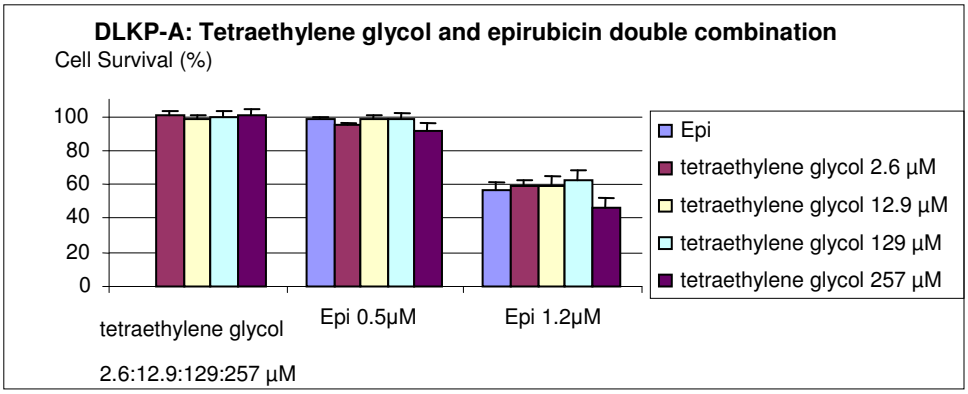
Graph 14: Repeat **343** *on DLKP-A with Epirubicin and Taxotere.*

Although the method had remained the same, the concentrations of the test compound, in this case **343**, and of Epirubicin used had been altered in the standard operating procedure. The solubility of **343** had not changed when using the same concentration of stock solution used as before, 10 mg/mL. The results of this examination provided two valued pieces of information; the first is that **343** and **346** had not been mixed when the first tests with these samples were carried out, as the results for this new batch of **343** are in agreement with those obtained from the original testing. Secondly is that **343** has been shown to work in combination with Taxotere which had not previously been carried out.

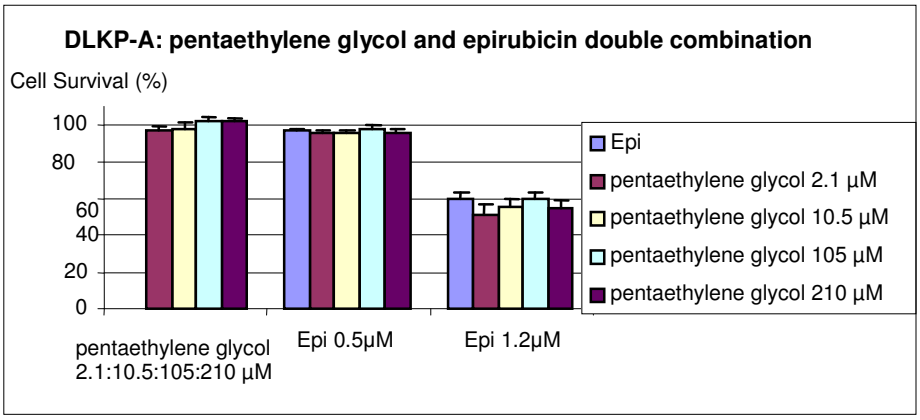
While the work was being carried out on **346** in an effort to obtain a solution of 10 mg/mL, a series of commercially available crown ethers and polyethylene glycols were also tested for their inhibition of P-gp. This was carried out for inclusion in the initial stages of a structure activity relationship study. The tested compounds were triethylene glycol, tetraethylene glycol, pentaethylene glycol, hexaethylene glycol, 15-crown-5 and benzo-18-crown-6 (non-toxic according to MSDS supplied by sigma-aldrich®). Of these compounds only benzo-18-crown-6 was seen to display a synergistic effect with epirubicin on the DLKP-A cell line. When the extent of the interaction is compared to that of **343**, **346** (original batch) and **357** in combination with epirubicin on the same cell line, it is clear that these have a much greater effect. Benzo-18-crown-6 only acts synergistically at 160 µM and above, whereas the required concentration of **357** is 40 µM and of **346** (original batch) lies between 2.5 µM and 12.5 µM. Graphs 15 to 20 illustrate the results of the testing of these six commercially available compounds.



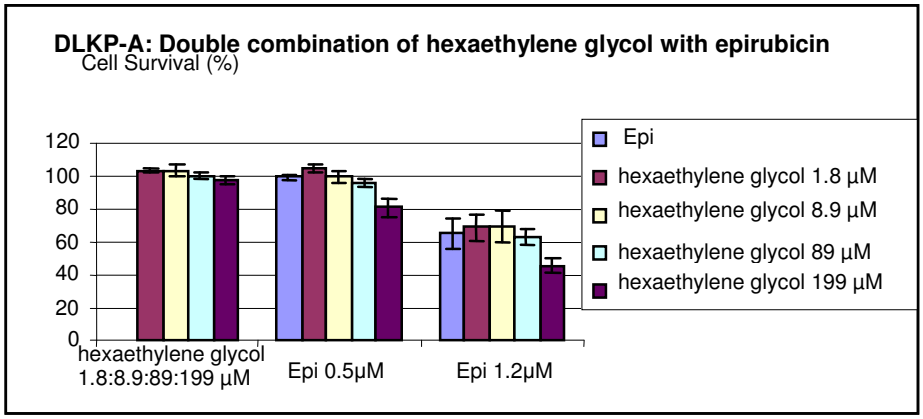
Graph 15: Double combination of triethylene glycol with epirubicin on the DLKP-A cell line



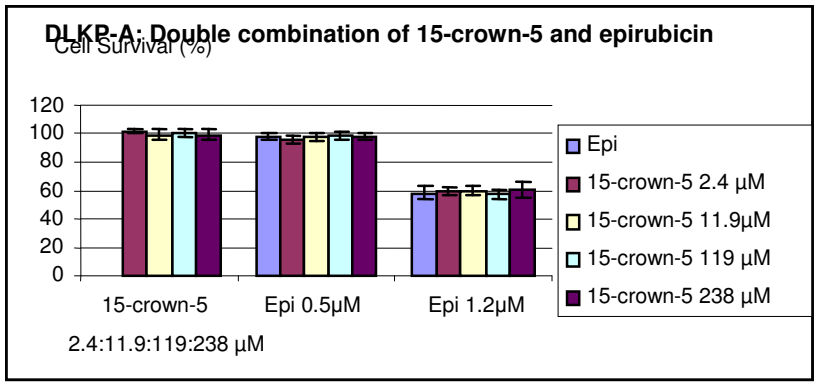
Graph 16: Double combination of tetraethylene glycol with epirubicin on the DLKP-A cell line



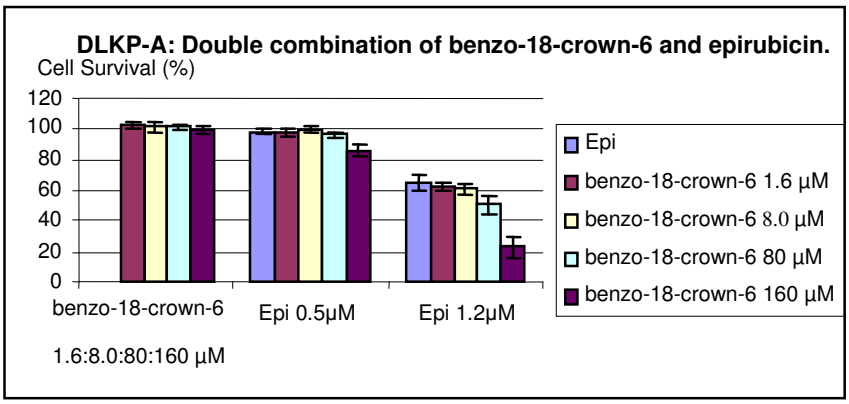
Graph 17: Double combination of pentaethylene glycol with epirubicin on the DLKP-A cell line



Graph 18: Double combination of hexaethylene glycol with epirubicin on the DLKP-A cell line



Graph 19: Double combination of 15-crown-5 with epirubicin on the DLKP-A cell line



Graph 20: Double combination of benzo-18-crown-6 with epirubicin on the DLKP-A cell line

The data obtained in this investigation is not a complete structure activity relationship study, nevertheless important information guiding future studies has been gained. It can be seen that the aromatic rings in the acyclic P-gp inhibitors are an important feature, although alone it does not indicate that similar compounds will act as P-gp inhibitors. The commercially available ethylene glycols tested do not have the aromatic

rings and show no effect on P-gp. **400,** which was synthesised within the group, also has no effect on P-gp. Each of the other acyclic products synthesised within the group that have been tested (**343**, **346**, **399**, **401** and **402**) had an effect on P-gp. **343**, **399** and **401** each displayed inhibition of P-gp. Although further testing proved the results from the initial testing of **346** were unreliable, it is still important to have aromatic rings in the structures of compounds within this group of P-gp inhibitors.

It also appears that the aromatic ring is important in the cyclic P-gp inhibitors; this is seen mainly with 15-crown-5 not inhibiting P-gp and benzo-18-crown-6 inhibiting P-gp although this difference could also be partly or entirely due to the difference in size of the ring.

Thus far in the SAR study it appears that the open structures are more effective as P-gp inhibitors than the macrocycles. Although to prove this conclusively it would be necessary to isolate and test **363** and a number of other macrocycles of varying size and constituents. Included in the testing of macrocycles should be analogues of **357** and **359** as well as macrocycles made from **399** and **401**.

Also the initial results from **343** compared to **346** point towards the finding that the structures being linked between the primary alcohols being more active than those linked between the phenols. However this is only a preliminary finding as can be seen in the difference in activity between **348** and **349** suggests the opposite to be true. These results taken together suggest that the position of the linker is important but which position is preferable depends on the linker molecule used. Therefore it is advisable when developing new acyclic P-gp inhibitors as part of the further work on this SAR study that each linker to be used should be tested when linked between the primary alcohols and when linked between the phenols.

5.3 Conclusion:

All compounds tested are non-toxic over the concentration ranges tested against *Pseudomonas aeruginosa, Escherichia coli, Klebsiella spp., Staphylococcus aureus, Salmonella spp., Enterococcus spp.* and *Bacillus subtilis*. This is a good indication that these compounds are relatively non-toxic to microbial life.

357 was shown to inhibit P-gp in DLKP-A cell line. From these results **343** was tested and **346** was synthesised and also investigated. **346** proved to be the most interesting potential P-gp inhibitor at this stage, due to its higher activity at lower concentrations. No further testing was carried out on **343** and **357** although they did exhibit inhibition

of P-gp on the DLKP-A cell line. The synthesis of **346** was then optimised so the confirmation studies could be carried out and also an investigation into how it inhibits P-gp. Each of the repeated synthesis of **346** lead to products that were insoluble at the required concentration in the biological media. In order to solve this problem a solution of **346** in ethanol with 15 % tween 80® was made, which stayed in solution on addition to the biological media. When this was analysed the activity of **346** could not be separated from the activity of the tween 80®.

It is apparent that the initial synthesis of **346** gave a product that differed in some way to each of the following syntheses, although all the data available suggests that the products are the same. The reason for this could be any number of factors including: a low level impurity: a difference in the structure of the product that is not evident: a difference in the crystal matrix of the product: or a difference in the biological media. The difference cannot be inspected any further as there is no remaining sample from the original synthesis of **346**, it was all consumed in the testing carried out.

If this project was to be continued in this direction the next step to be taken would be to have the analysis on **357** and **343** repeated to confirm the results. Then, using these two compounds as the starting point, carry out a structure activity relationship study to both identify the pharmocophore and to develop a product with higher activity as a P-gp inhibitor. The information obtained from the testing of each of the commercially available compounds and compounds **346**-**349** can also be added to the structure activity relationship study. Included in this study should be the synthesis and isolation of **363** (chapter 2) and any possible decomposition products from **357**. As the results from the initial batch of **346** could not be repeated there is no information from this compound to aide in the structure activity relationship study. As these products are made and tested further information on structural characteristics which help increase P-gp inhibition will be gained. This information can be used to aide the development of a more effective P-gp inhibitor.

Experimental:

Synthesis of **346** was carried out using two methods, the original method used and the optimised method. The original synthesis was repeated multiple times, each time changing the work up as detailed in table 51. The product of each different work up was characterised by NMR and MP before attempts were made to dissolve these products in ethanol at 10 mg/mL.

Minimum inhibitory concentration (toxicity) testing was carried out by Dr. Brid Quilty in the school of biotechnology, Dublin City University.

P-gp inhibition testing carried out by Aoife Devery, under the supervision of Dr Robert O'Connor of the National Institute of Cellular Biotechnology, Dublin City University.

Minimum inhibitory concentration testing:

Minimum inhibitory concentrations (MICs) for the compounds were determined by serial two-fold dilutions in Mueller-Hinton broth using the broth micro-dilution method described by Amsterdam.[80]

The bacterial strains were grown in Mueller-Hinton broth overnight. The compound to be tested was dissolved in sterile water and diluted in the test medium to 4000 μg/mL. 100 μL of Mueller-Hinton broth was dispensed into all wells of a microtitre plate. 100 μL of the compound solution was measured into the wells in column 1 (far left of plate). The compound was mixed into the wells in column 1 by pumping the pipette up and down 6-8 times. 100 μL was withdrawn from column 1 and added to column 2. This made column 2 a two-fold dilution of column 1 and again was mixed by pumping the pipette up and down 6-8 times. 100 μL was transferred to column 3. This procedure was repeated down to column 10 only. 100 μL was discarded from column 10 rather than putting it in column 11. 5 μL of (2×10^4 CFU/mL) the strain to be tested was dispensed into wells in the columns 11 to 1 in that order. Column 12 was used as a sterility control. The plates were incubated at 37 °C. Growth on the plates was noted and recorded after 18-36 hours. The MIC was the lowest concentration of the compound that completely inhibited growth of the organism in the micro-dilution wells as detected by the unaided eye.

Compounds that were water-insoluble were diluted in methanol. The MICs for these compounds were obtained using the same procedure described above. However, instead of diluting the compound directly in Mueller-Hinton broth, 20 μL of the solution (to give a final concentration of 20000 μg/mL) was added to the first well in the row. The methanol was allowed to evaporate and then 200 μL of Mueller-Hinton broth was added, mixed and diluted using serial two-fold dilutions as described above.

P-gp inhibition testing:

Solubilisation of the compounds:

The test compound (10 mg) was placed into a vial. DMSO (1 mL), ethanol (1 mL) or water (1 mL) was added and the vial was shaken vigorously. The vial was then sonicated at 37 ^{o}C for 1 hour.

If the compound was dissolved at this stage it was tested for its solubility in cell culture complete media (10 µL of the test solution in 40 µL of complete media or a dilution to make up 100 µM was carried out).

Assessment of cell number by the acid phosphatase assay

Following the incubation period of 6-7 days, media was removed from the plates. Each well was washed twice with phosphate buffered saline (100 µL). This was then removed and freshly prepared phosphatase substrate (100 µL) (10 mM *p*-nitrophenol phosphate in 0.1 M sodium acetate, 0.1 % triton X-100 (pH 5.5)) was added to each well. The plates were then incubated in the dark at 37 ^{o}C for 2 hours. The enzymatic reaction was stopped by the addition of 1N NaOH (50 µL). The plate was read in a dual beam plate reader (Synergy HT, Bio-Tek, USA) at 450nm with a reference wavelength of 620 nm.

Initial combination toxicity assays

Each compound to be tested was diluted to the relevant concentrations for testing. The first double combination to be carried out was with epirubicin and if an interesting result was found the double combinations was repeated with taxotere and 5-FU.

The plates were incubated for 6 days, at which time the acid phosphatase assay was carried out in order to determine the cell density.

Results from this method gave information on the compounds short term stability in culture conditions, of its general toxicity and whether a synergistic combination with epirubicin was possible on either the DLKP or DLKP-A cell lines.

***In vitro* toxicity assays**

Cell suspensions containing 10^4 cell/mL were prepared in a cell culture medium. These cell suspensions (100 µL/well) were added to 96-well plates. Plates were agitated gently in order to ensure even dispersion of cells over a given well. Cells were then incubated overnight at 37 ^{o}C in an atmosphere containing 5 % CO_2. Cytotoxic drug

dilutions were prepared at double their final concentration in cell culture medium. Volumes of the drug dilutions (100 µL) were then added to each well. Plates were then mixed gently as above. Cells were incubated for a further 5 days at 37 ^{o}C and 5 % CO_2 until the control wells had reached approximately 80-90 % confluency. Assessment of cell survival in the presence of drug was determined by the acid phosphatase assay.

Combination toxicity assays

The 96-well plates were seeded as described above and incubated overnight at 37 ^{o}C with 5 % CO_2. Dilutions of cytotoxic drugs and other agents were prepared at 4X their final concentration in media. The drug solution (50 µL) and the combination drug solution (50 µL) were then added to each relevant well so that each well had a final volume of 200 µL. All potential toxicity-enhancing agents were dissolved in DMSO, ethanol or media. Stock solutions (approximately 1.5 mg/mL) were prepared in media; the filter was sterilised with a 0.22 µm filter and then used to prepare all subsequent dilutions. Cells were incubated for a further 5 days at 37 ^{o}C in an atmosphere of 5 % CO_2. At this point the control wells would have reached approximately 80-90 % confluency. Cell number was assessed using acid phosphatase assay.

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Conclusion

In conclusion a number of new precursors to macrocycles, each containing 2-(2-hydroxyethoxy)phenol, were synthesised. These precursors were then successfully used in the synthesis of novel macrocycles. The possibility of the optimisation of the synthesis of these macrocycles was shown with the optimisation of **353**.

A number of new precursors to macrocycles, each containing morphine in place of 2-(2-hydroxyethoxy)phenol, were also synthesised. These precursors were then used in the attempted generation of novel macrocycles. Although the isolation of the macrocycles containing morphine was unsuccessful, steps were taken that will contribute to the research of the group as further efforts are made at the isolation of these compounds.

Each of the synthesised compounds were tested for metal extraction with some success. Cobalt picrate was only extracted by compound **344** and strontium picrate was only extracted by compound **340**. The most interesting result from this analysis was the selective extraction of copper picrate by **352**.

A selection of the macrocycles and their precursors containing 2-(2-hydroxyethoxy)phenol were subjected to toxicity testing against *Pseudomonas aeruginosa, Escherichia coli, Klebsiella spp., Staphylococcus aureus, Salmonella spp., Enterococcus spp.* and *Bacillus subtilis*. All compounds were found to be non-toxic over the concentration range 0-2000 μg per mL.

A number of the products of this project were tested for inhibition of P-gp. There were preliminary positive results. **346** gave the most impressive result of these but its results were not repeatable. There were other positive results but due to the thorough investigation of **346** these results were not fully scrutinised. This work will be the basis of a structural activity study which will be continued within the research group.

The initial goal of this project was the synthesis of the macrocycles containing morphine. Although the attempts at this were not successful the study will be continued within the research group using the results in this project as a guide. New P-gp inhibitors have been developed and investigation of this will also be continued within the research group in an effort to develop a more efficient inhibitor.

APPENDIX 1

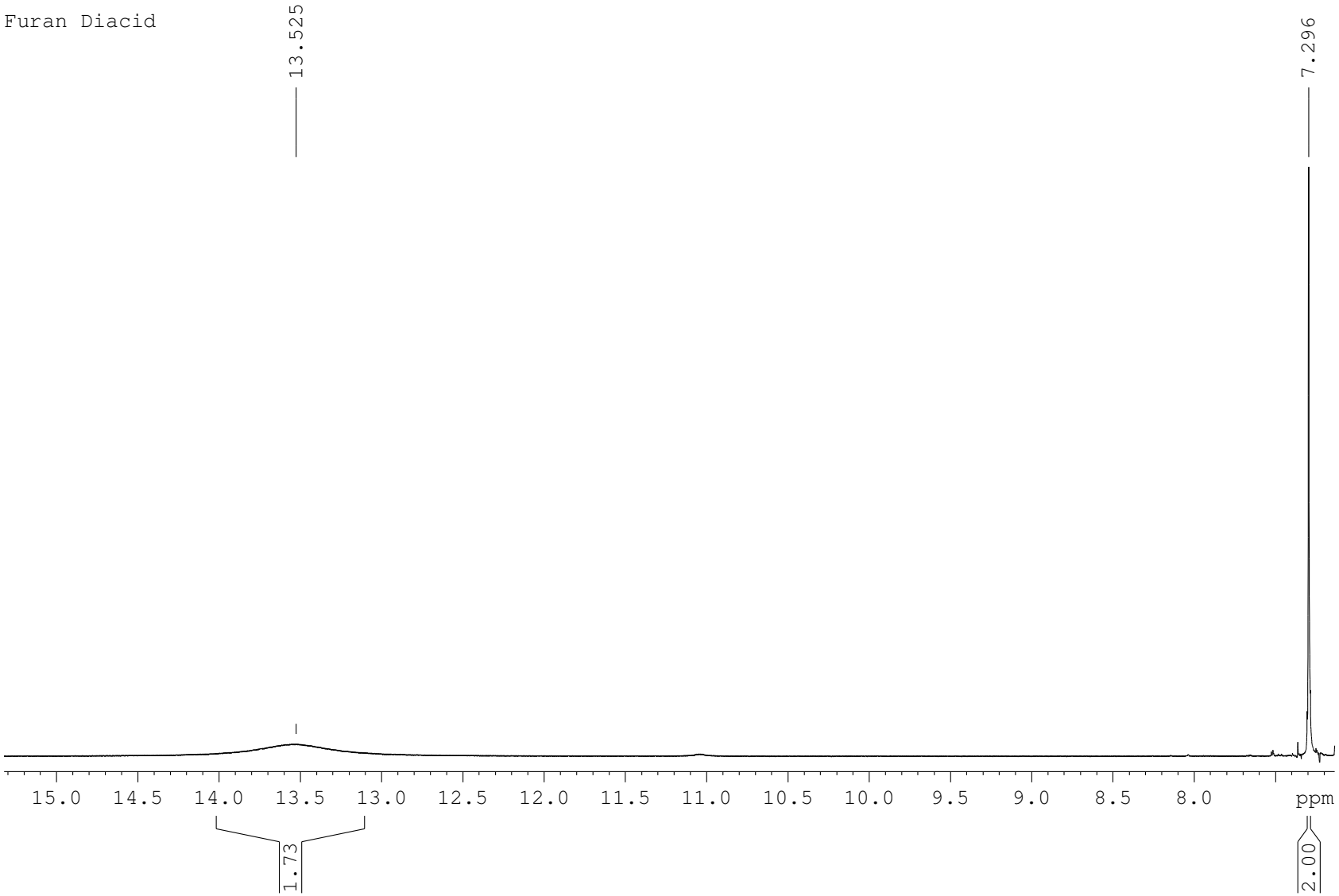
NMR spectra

Compound: **337**

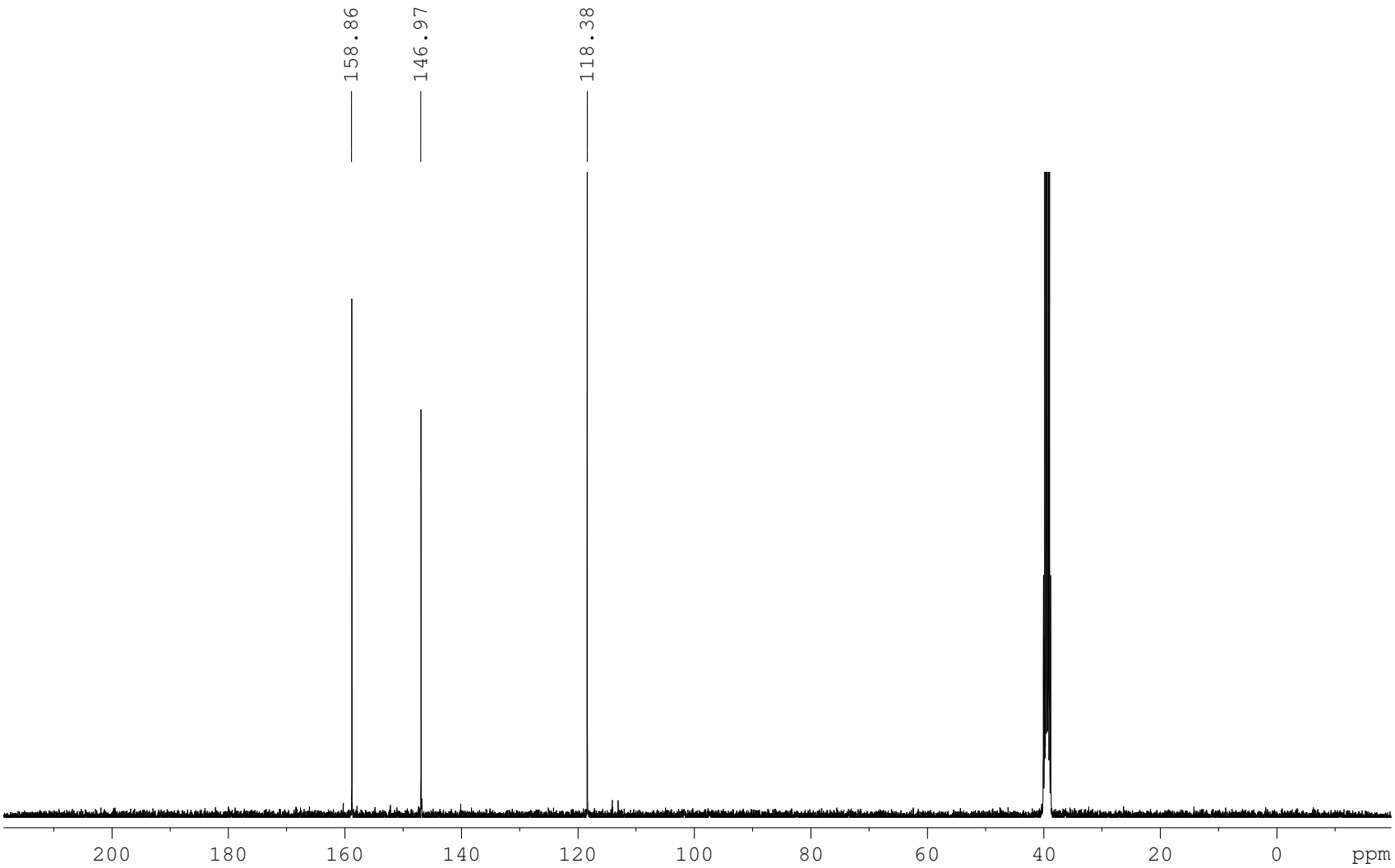
Furan-2,5-dicarbonyl dichloride

^{1}H and ^{13}C NMR

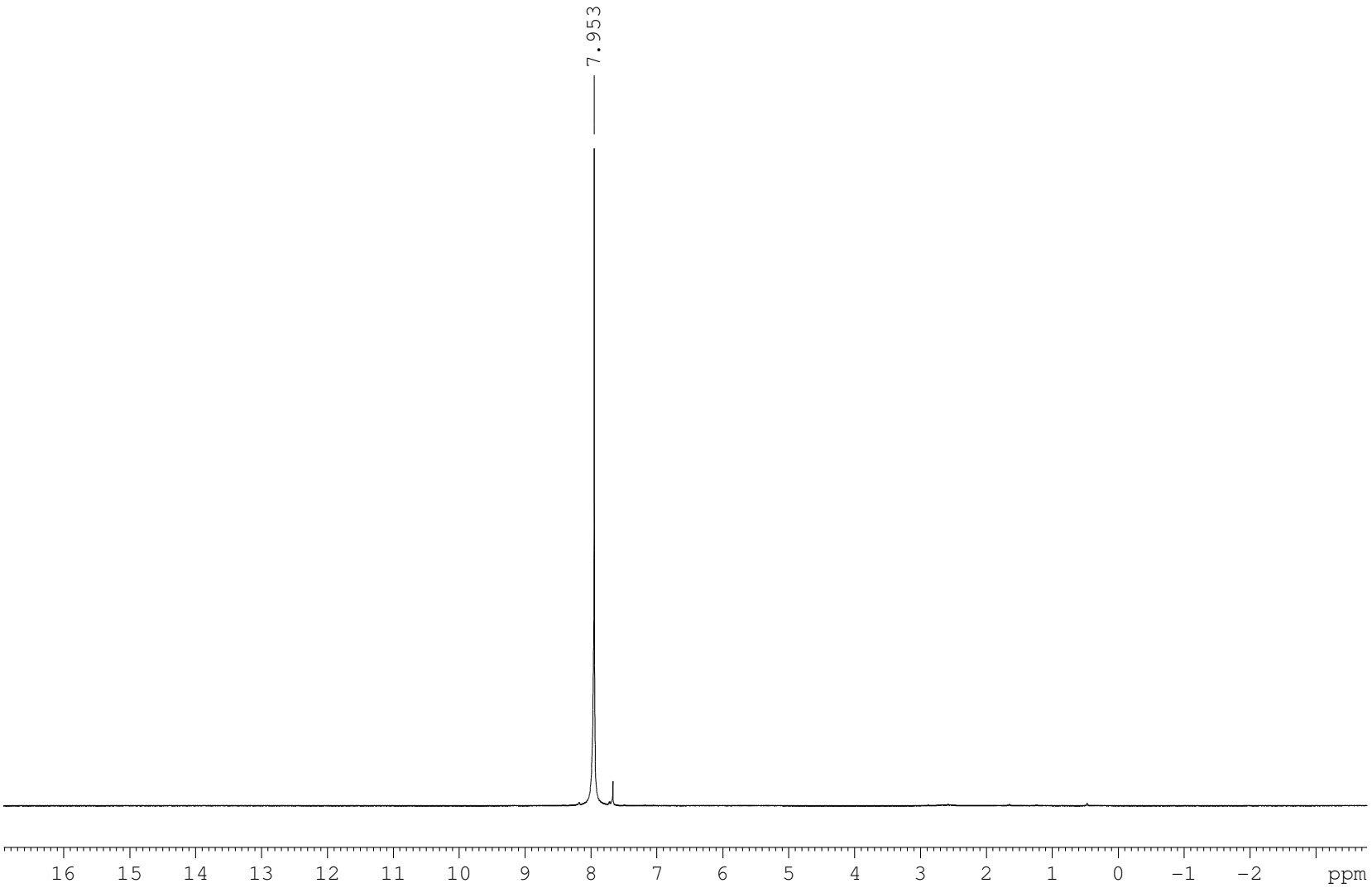
Furan Diacid



Furan-2,5-diacid



Furan Dichloride



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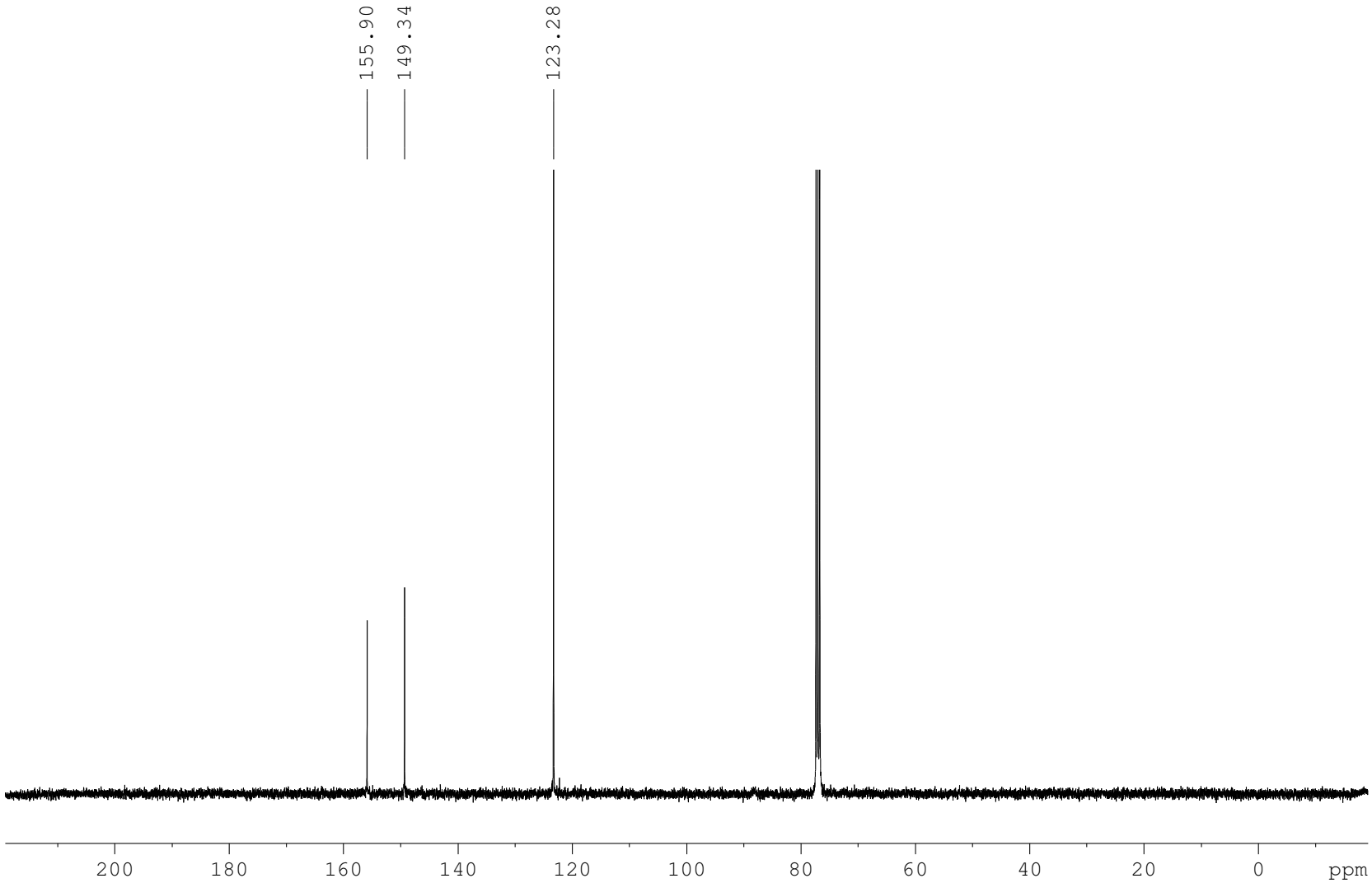
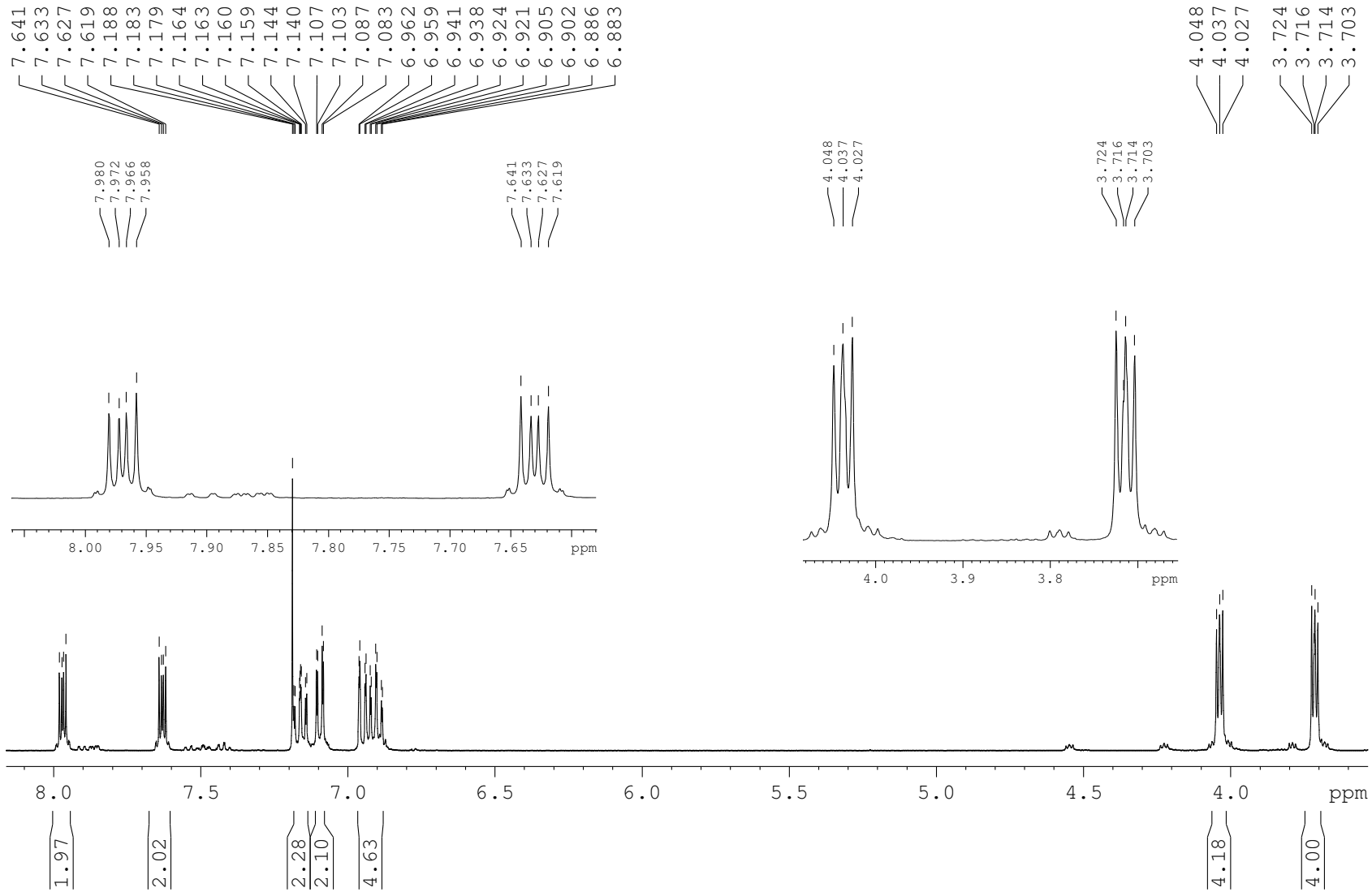


Compound: **338**

Bis(2-(2-Hydroxyethoxy)phenyl)phthalate

^{1}H and ^{13}C NMR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7.159
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7.107
7.103
7.087
7.083
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6.959
6.941
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6.905
6.902
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6.883
4.048
4.037
4.027
3.724
3.716
3.714
3.703
7.980
7.972
7.966
7.958
7.641
7.633
7.627
7.619
8.00
7.95
7.90
7.85
7.80
7.75
7.70
7.65
ppm
4.0
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3.8
ppm
8.0
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7.0
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ppm
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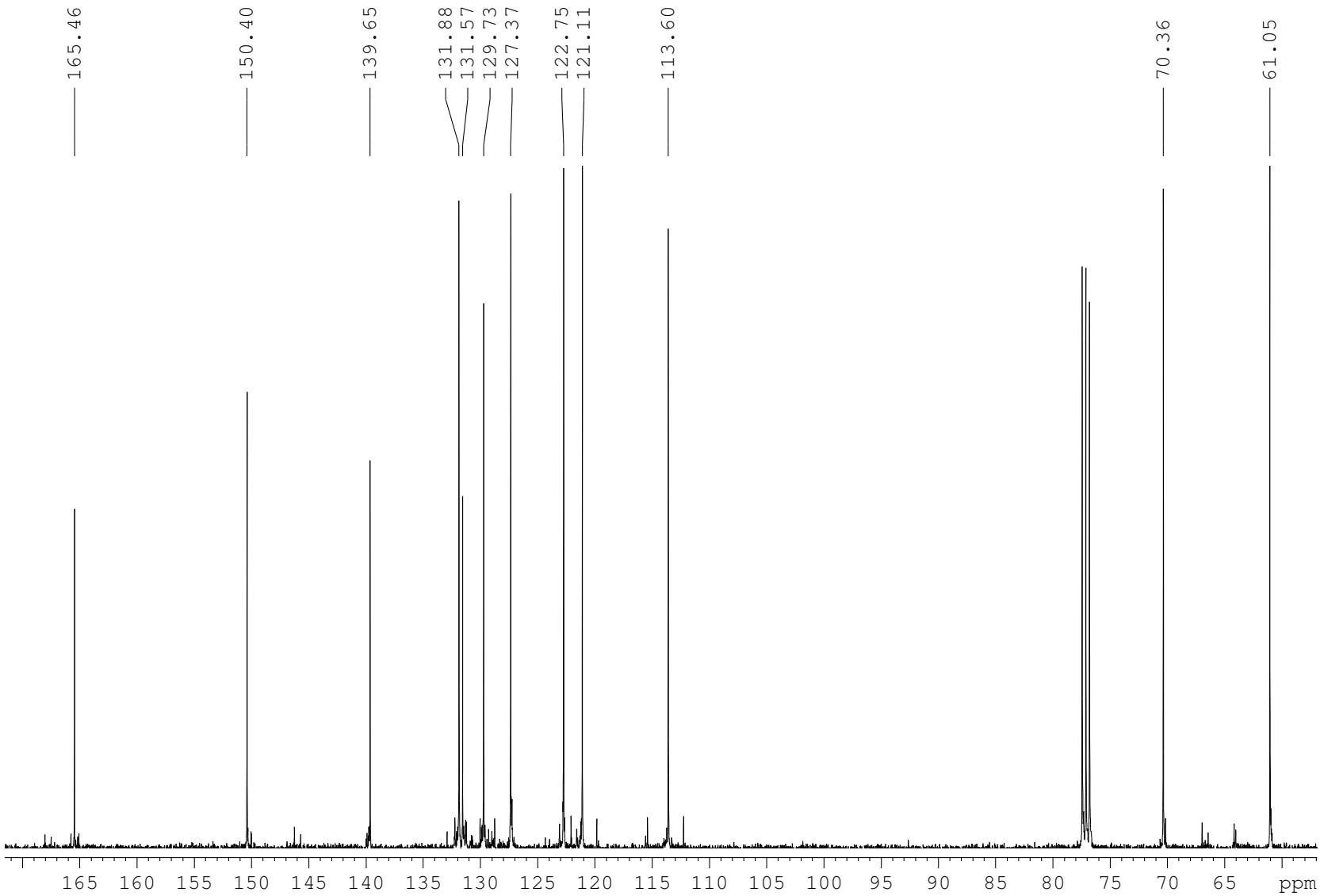
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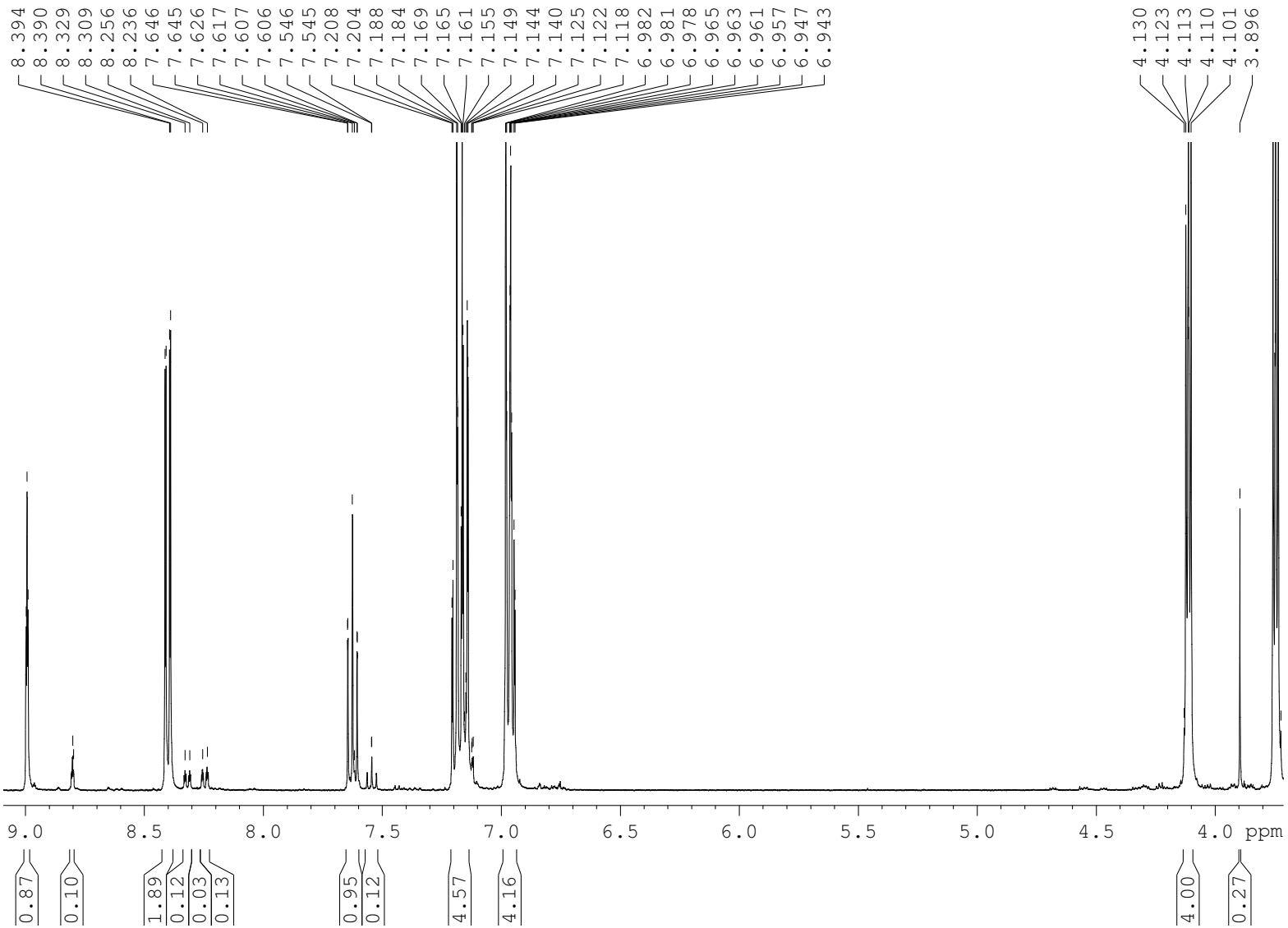
131.57
129.73
127.37
122.75
121.11
113.60
70.36
61.05
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65
ppm

Compound: **339**

Bis(2-(2-Hydroxyethoxy)phenyl)isophthalate

^{1}H and ^{13}C NMR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6.963
6.961
6.957
6.947
6.943
4.130
4.123
4.113
4.110
4.101
3.896
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8.0
7.5
7.0
6.5
6.0
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5.0
4.5
4.0 ppm
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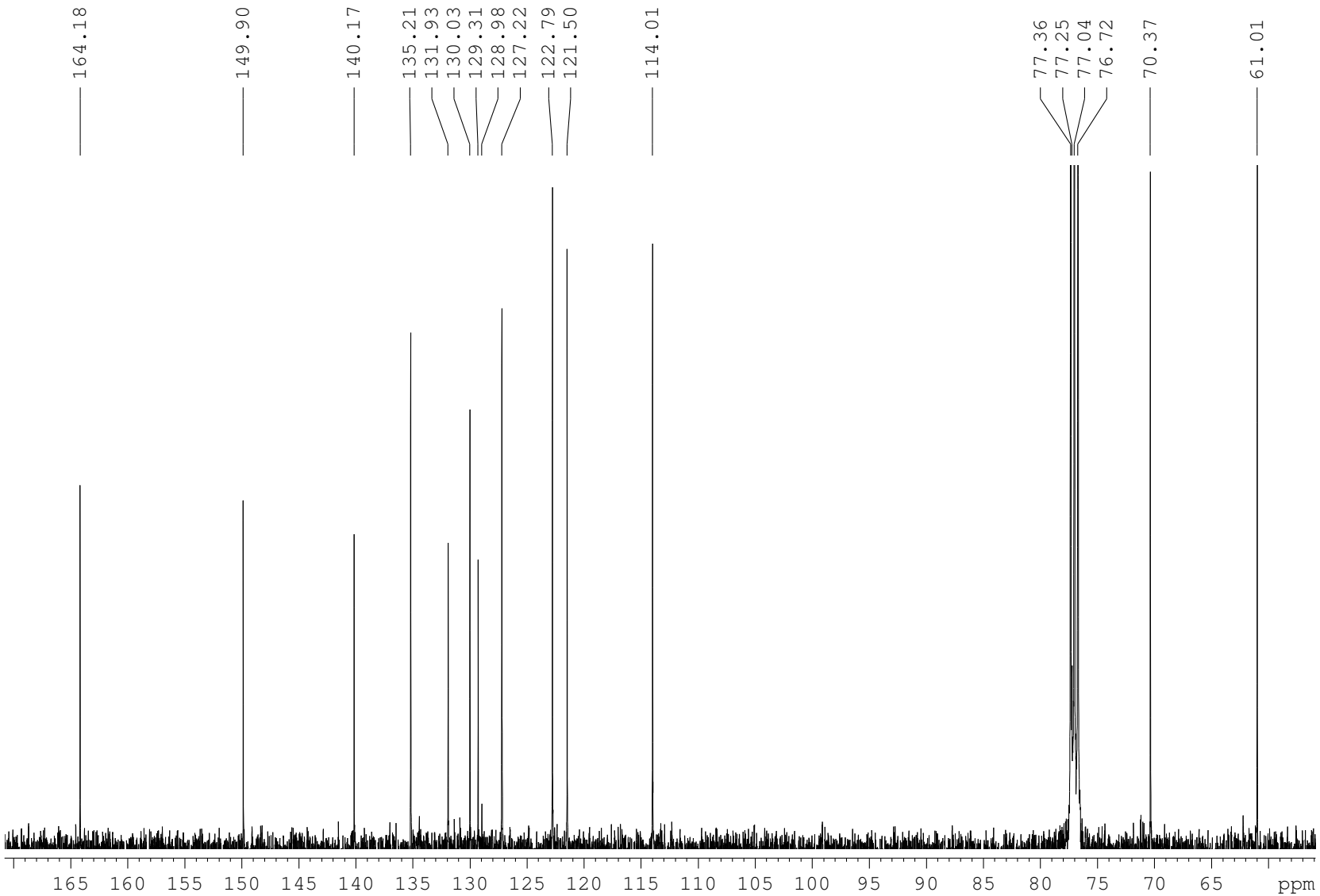
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129.31
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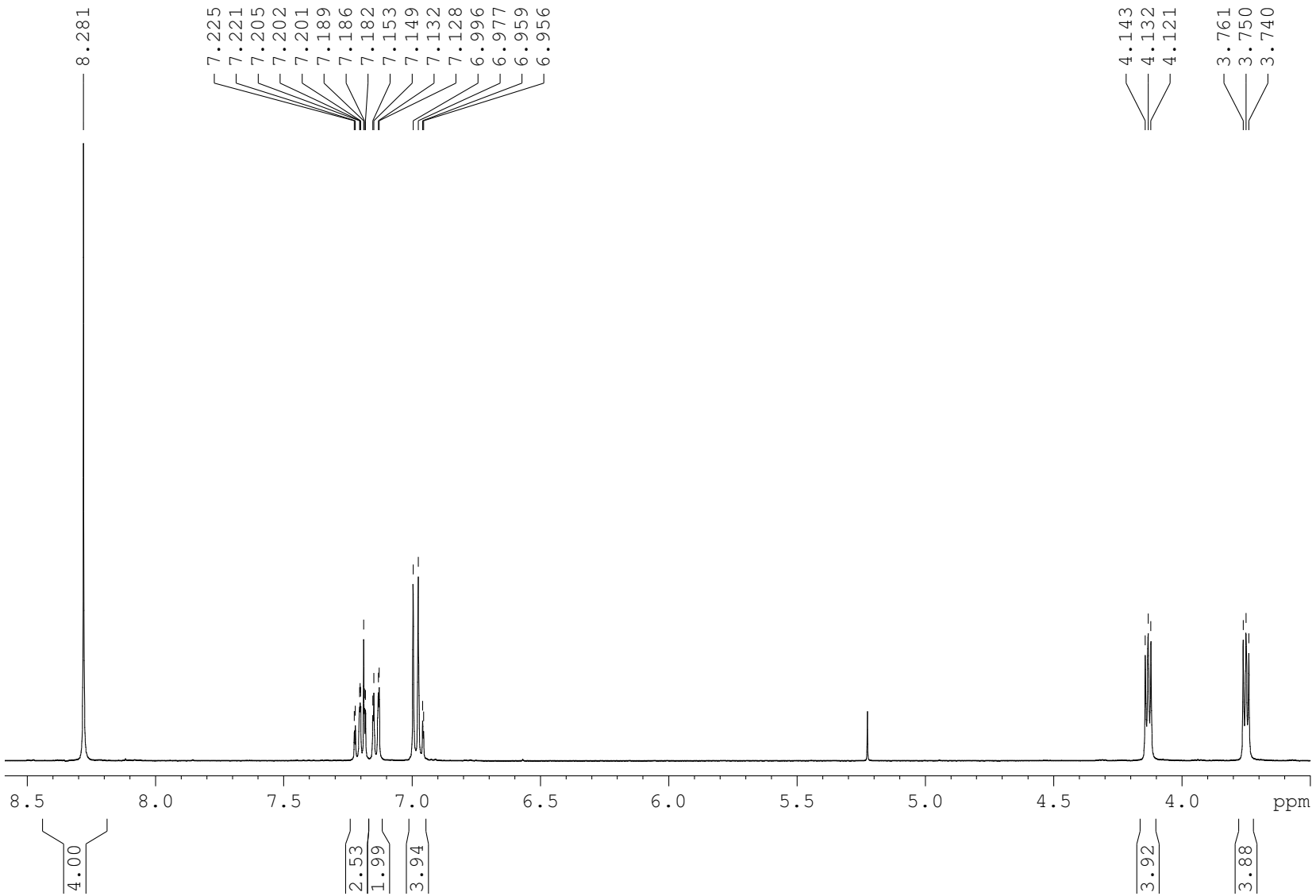
127.22
122.79
121.50
114.01
77.36
77.25
77.04
76.72
70.37
61.01
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65
ppm

Compound: **340**

Bis(2-(2-Hydroxyethoxy)phenyl)terephthalate

^{1}H and ^{13}C NMR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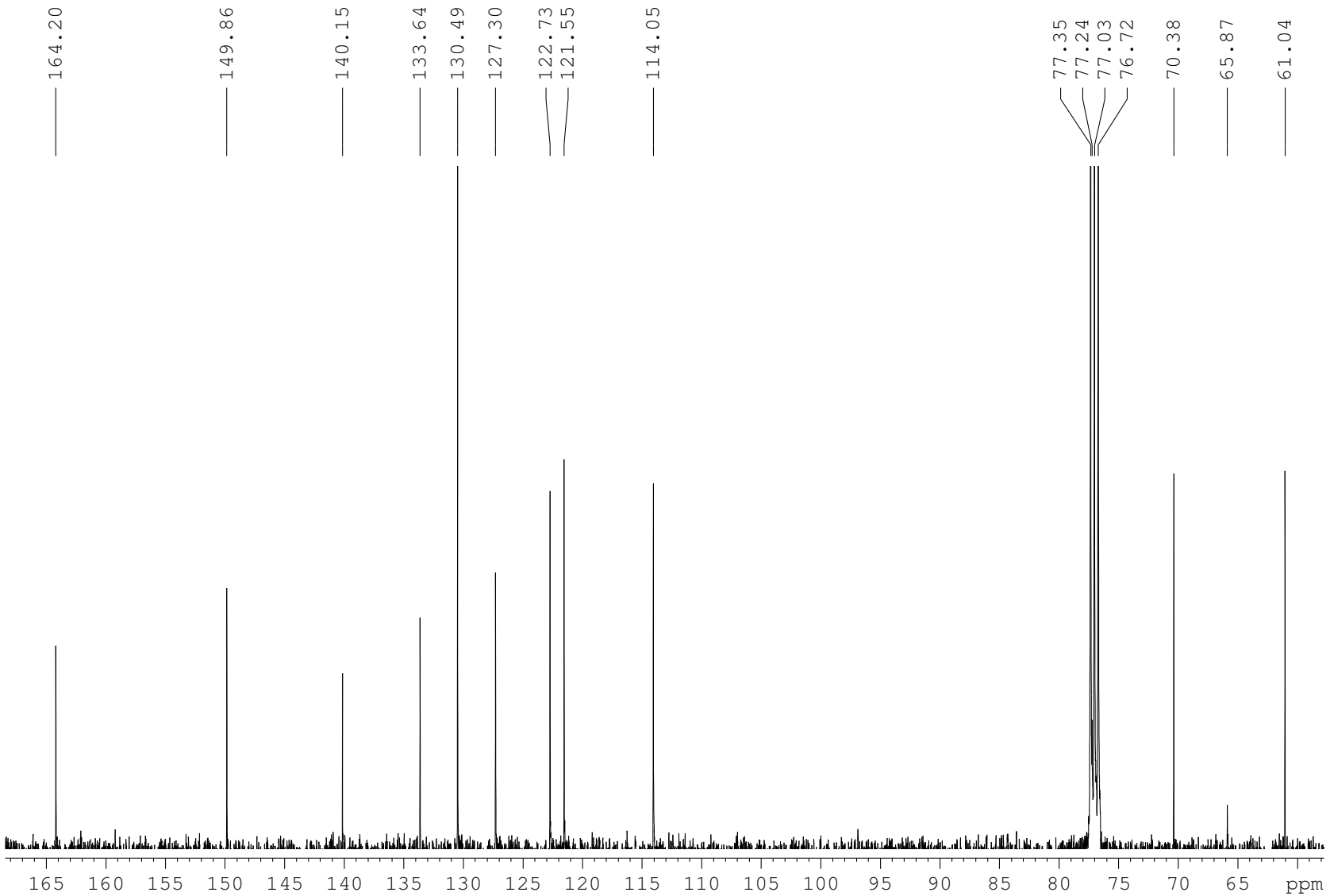
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130.49
127.30
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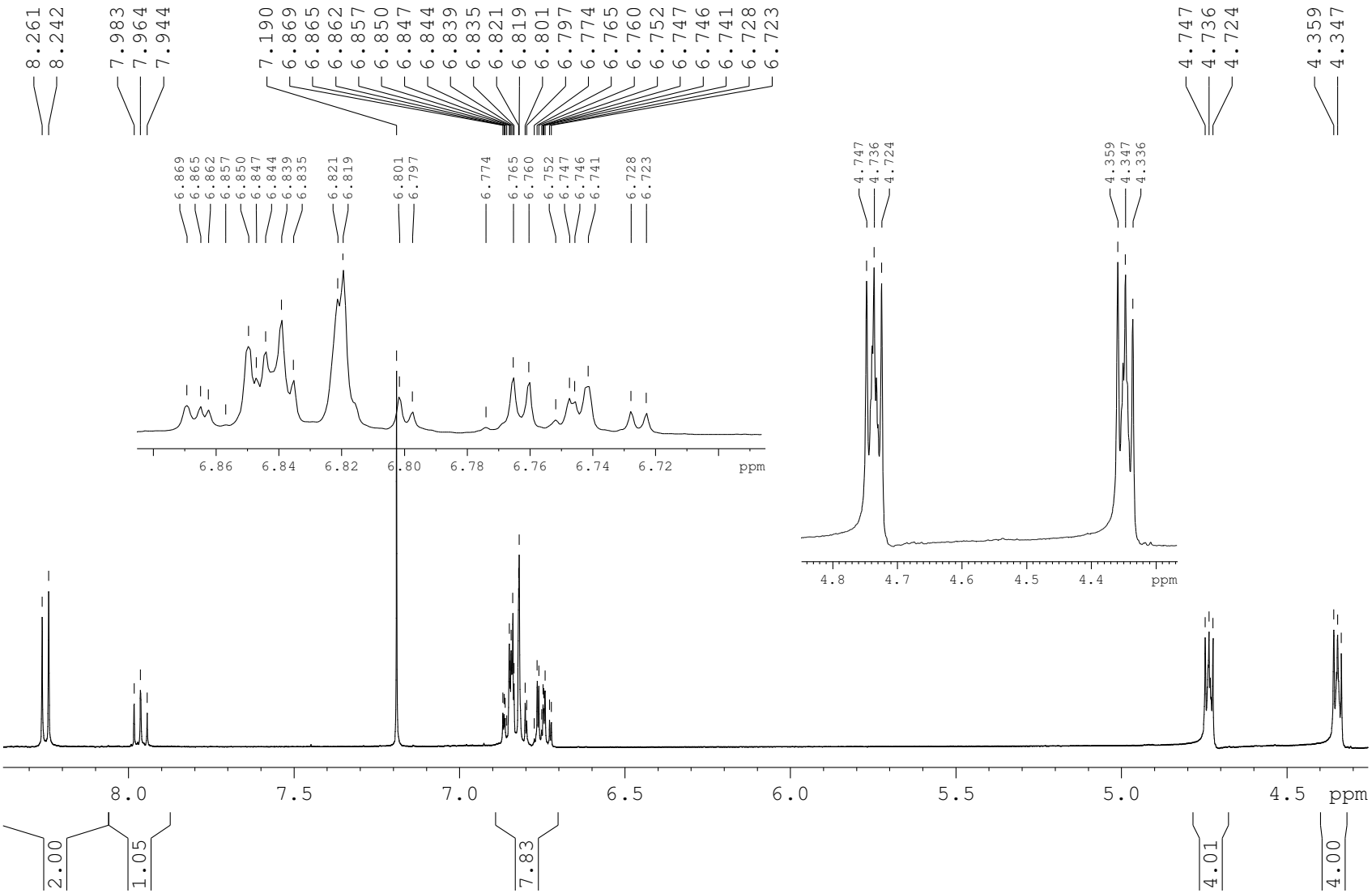
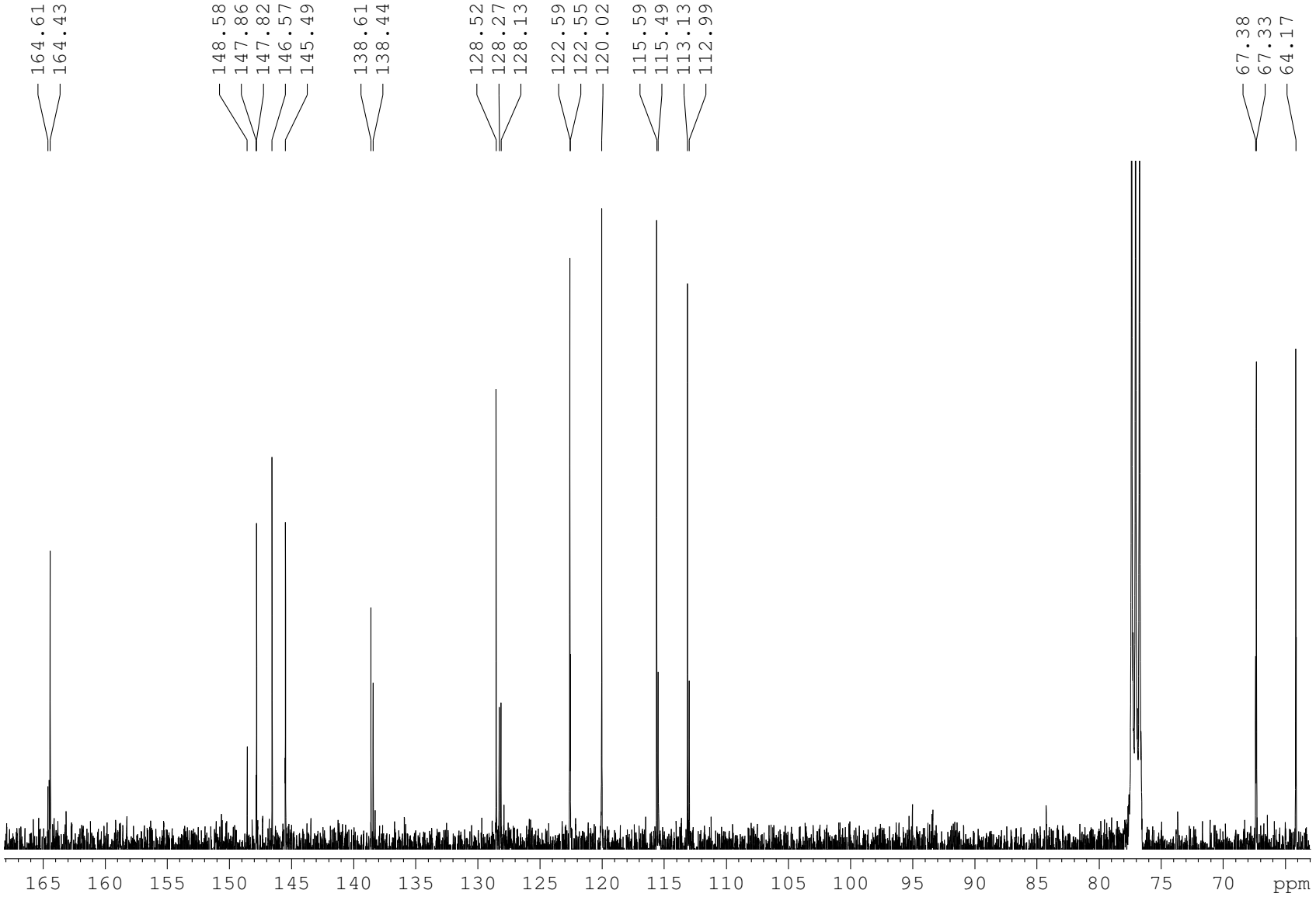
121.55
114.05
77.35
77.24
77.03
76.72
70.38
65.87
61.04
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 ppm

Compound: **341**

Bis(2-(2-Hydroxyethoxy)phenyl)pyridine-2,6-dicarboxylate

^{1}H and ^{13}C NMR

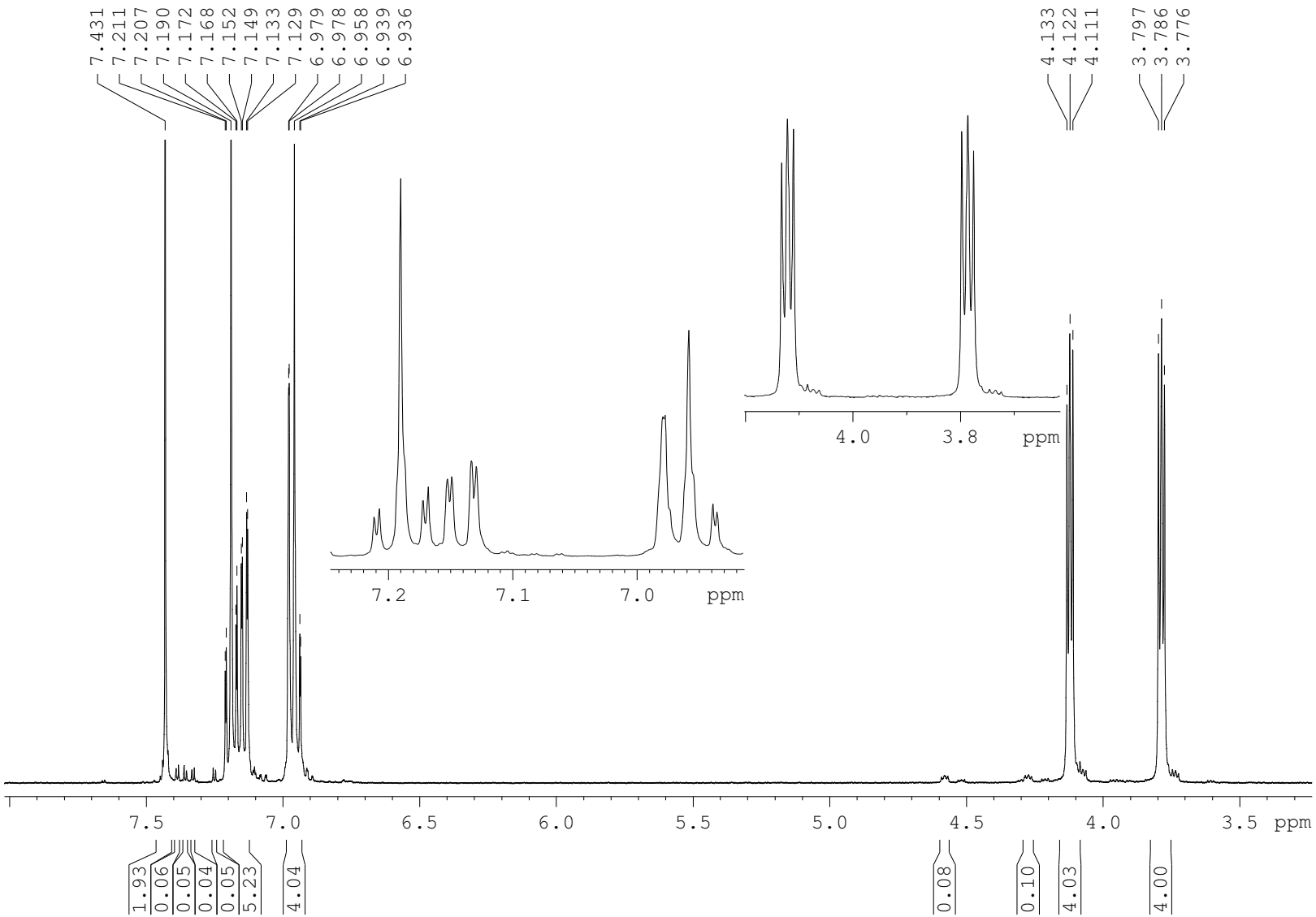

8.261
8.242
7.983
7.964
7.944
7.190
6.869
6.865
6.862
6.857
6.850
6.847
6.844
6.839
6.835
6.821
6.819
6.801
6.797
6.774
6.765
6.760
6.752
6.747
6.746
6.741
6.728
6.723
4.747
4.736
4.724
4.359
4.347
6.86
6.84
6.82
6.80
6.78
6.76
6.74
6.72
ppm
4.8
4.7
4.6
4.5
4.4
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm
2.00
1.05
7.83
4.01
4.00

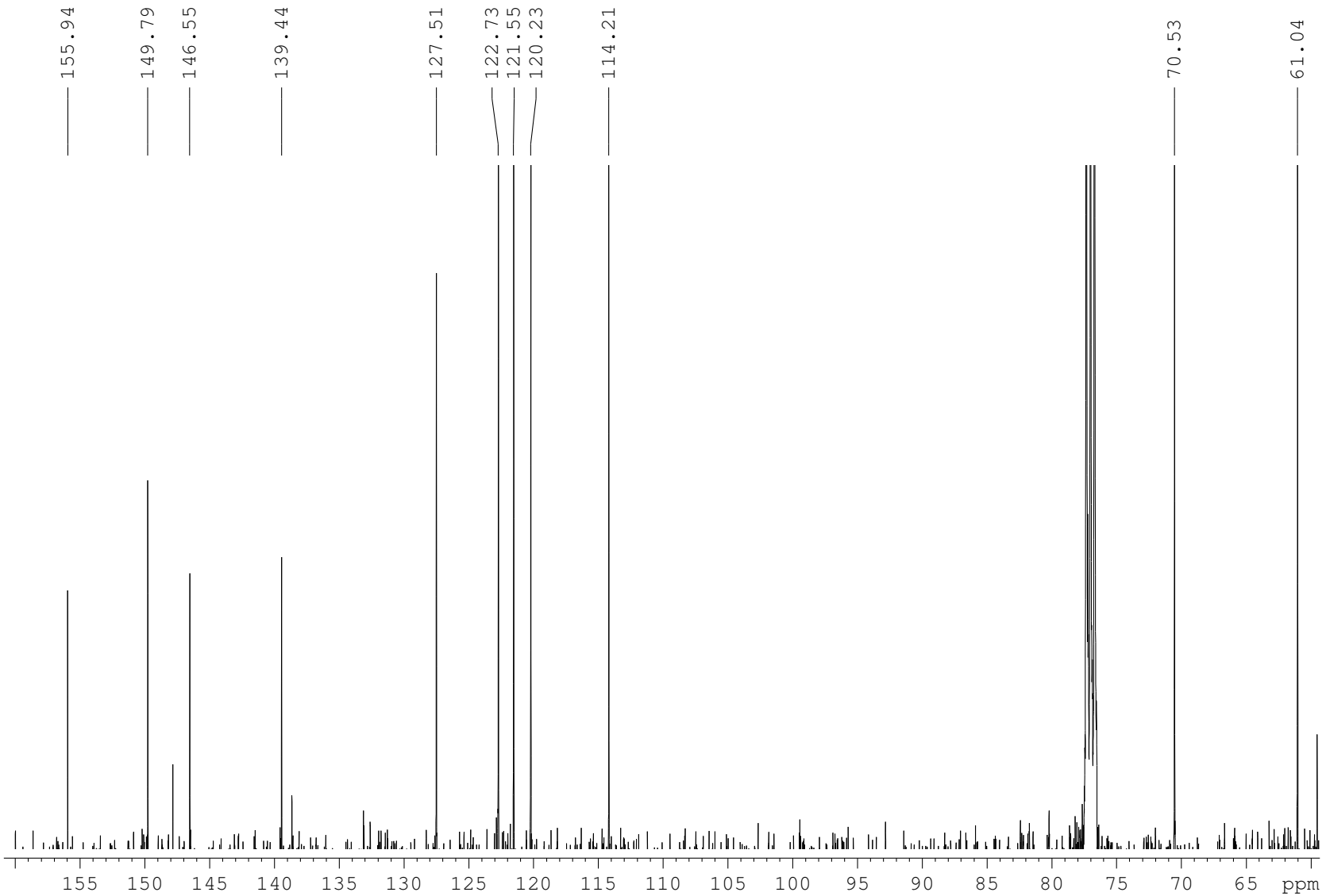

164.61
164.43
148.58
147.86
147.82
146.57
145.49
138.61
138.44
128.52
128.27
128.13
122.59
122.55
120.02
115.59
115.49
113.13
112.99
67.38
67.33
64.17
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 ppm

Compound: **342**

Bis(2-(2-Hydroxyethoxy)phenyl)furan-2,5-dicarboxylate

^{1}H and ^{13}C NMR

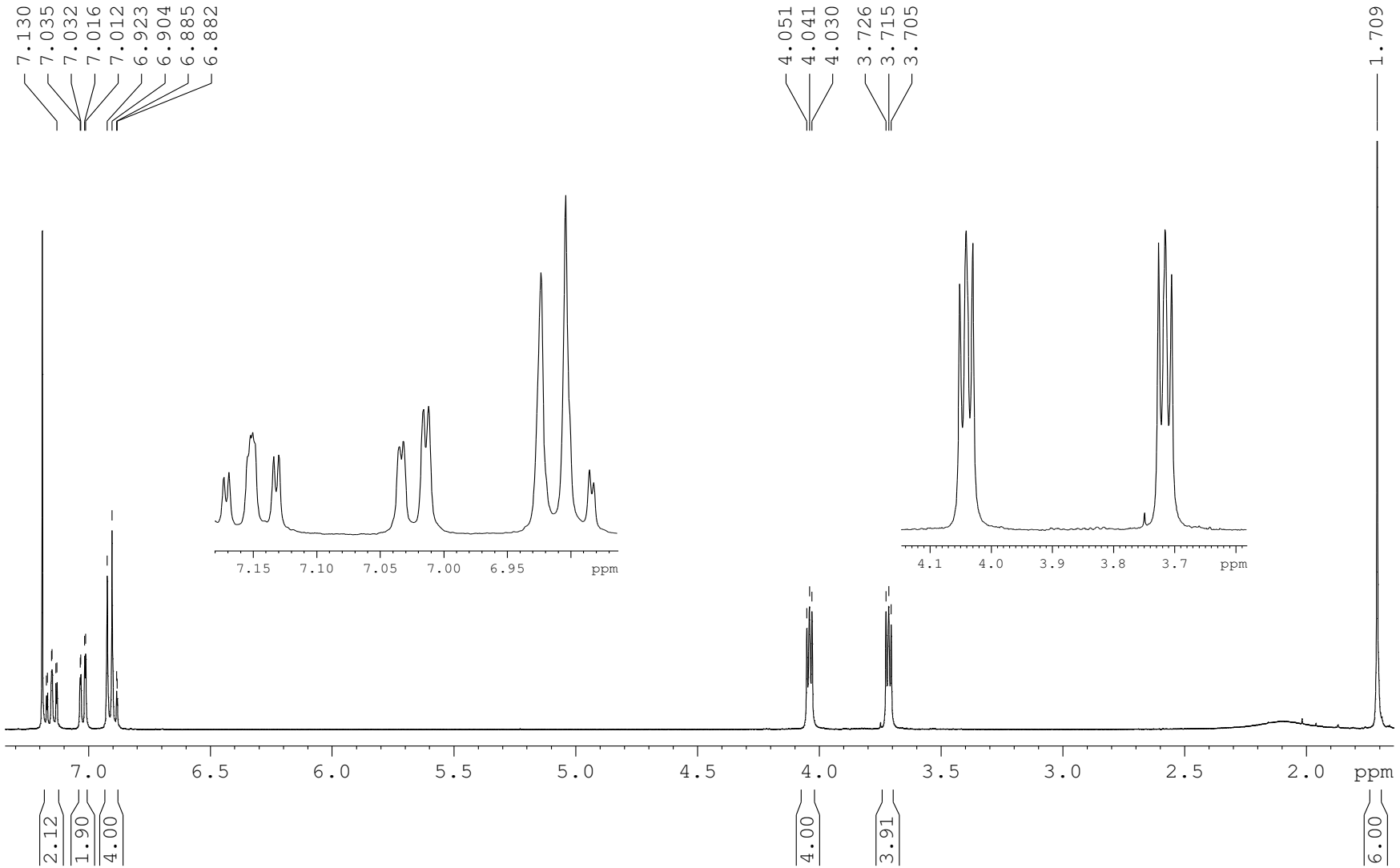

7.431
7.211
7.207
7.190
7.172
7.168
7.152
7.149
7.133
7.129
6.979
6.978
6.958
6.939
6.936
4.133
4.122
4.111
3.797
3.786
3.776
7.2
7.1
7.0
ppm
4.0
3.8
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm
1.93
0.06
0.05
0.04
0.05
5.23
4.04
0.08
0.10
4.03
4.00

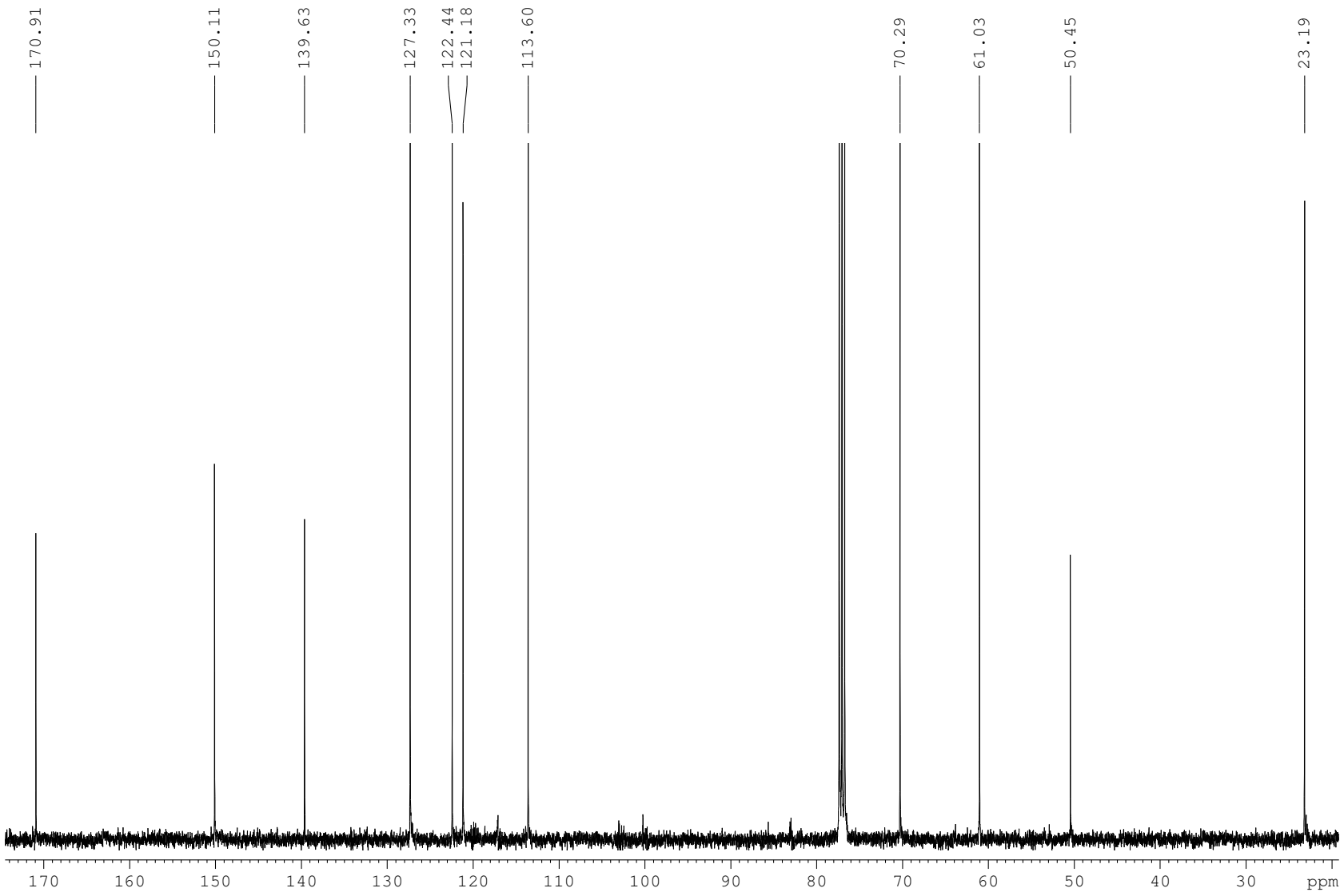

155.94
149.79
146.55
139.44
127.51
122.73
121.55
120.23
114.21
70.53
61.04
155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 ppm

Compound: **343**

Bis(2-(2-Hydroxyethoxy)phenyl)-2,2-dimethylmalonate

^{1}H and ^{13}C NMR

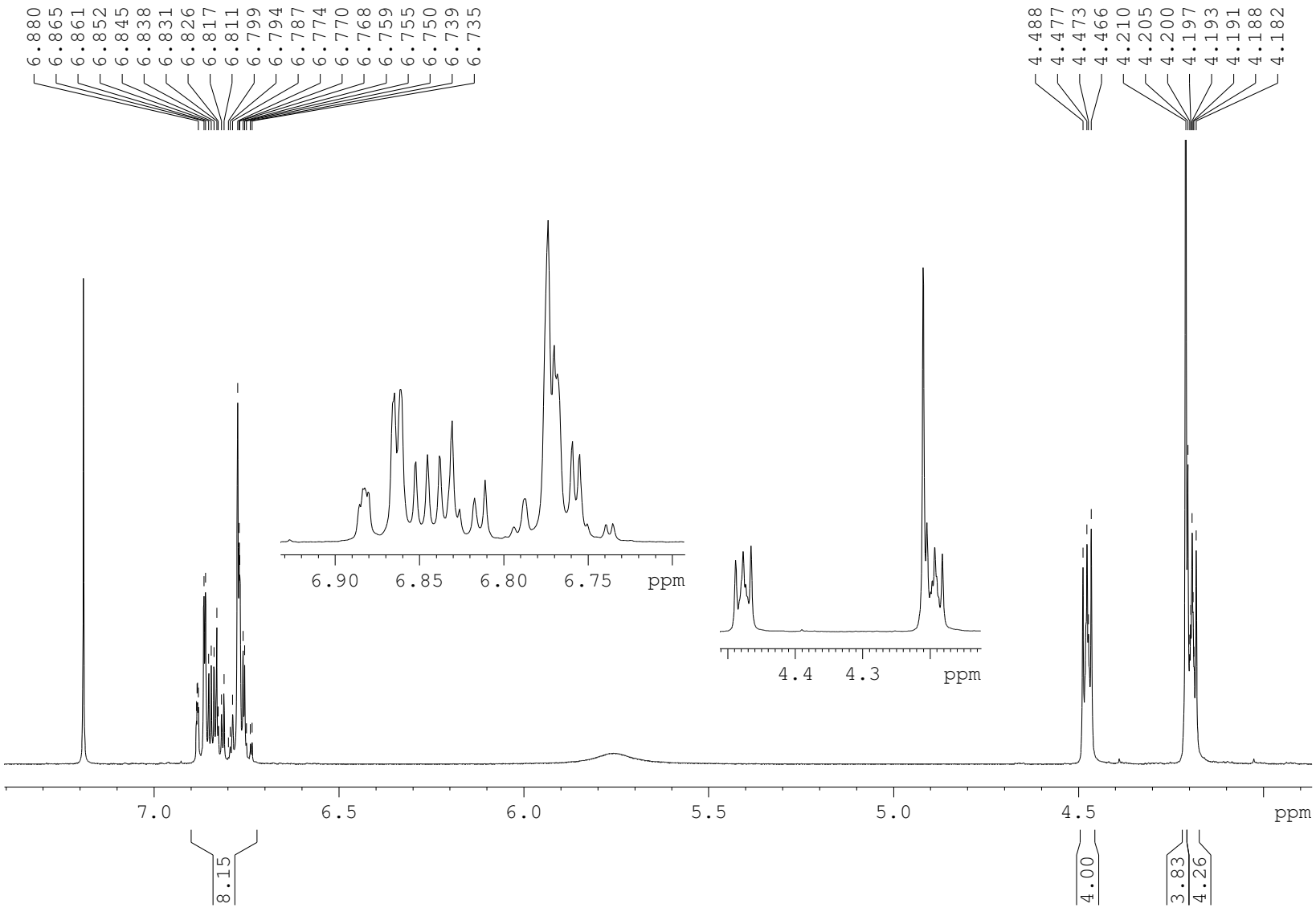

7.130
7.035
7.032
7.016
7.012
6.923
6.904
6.885
6.882
4.051
4.041
4.030
3.726
3.715
3.705
1.709
7.15
7.10
7.05
7.00
6.95
ppm
4.1
4.0
3.9
3.8
3.7
ppm
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
2.12
1.90
4.00
4.00
3.91
6.00

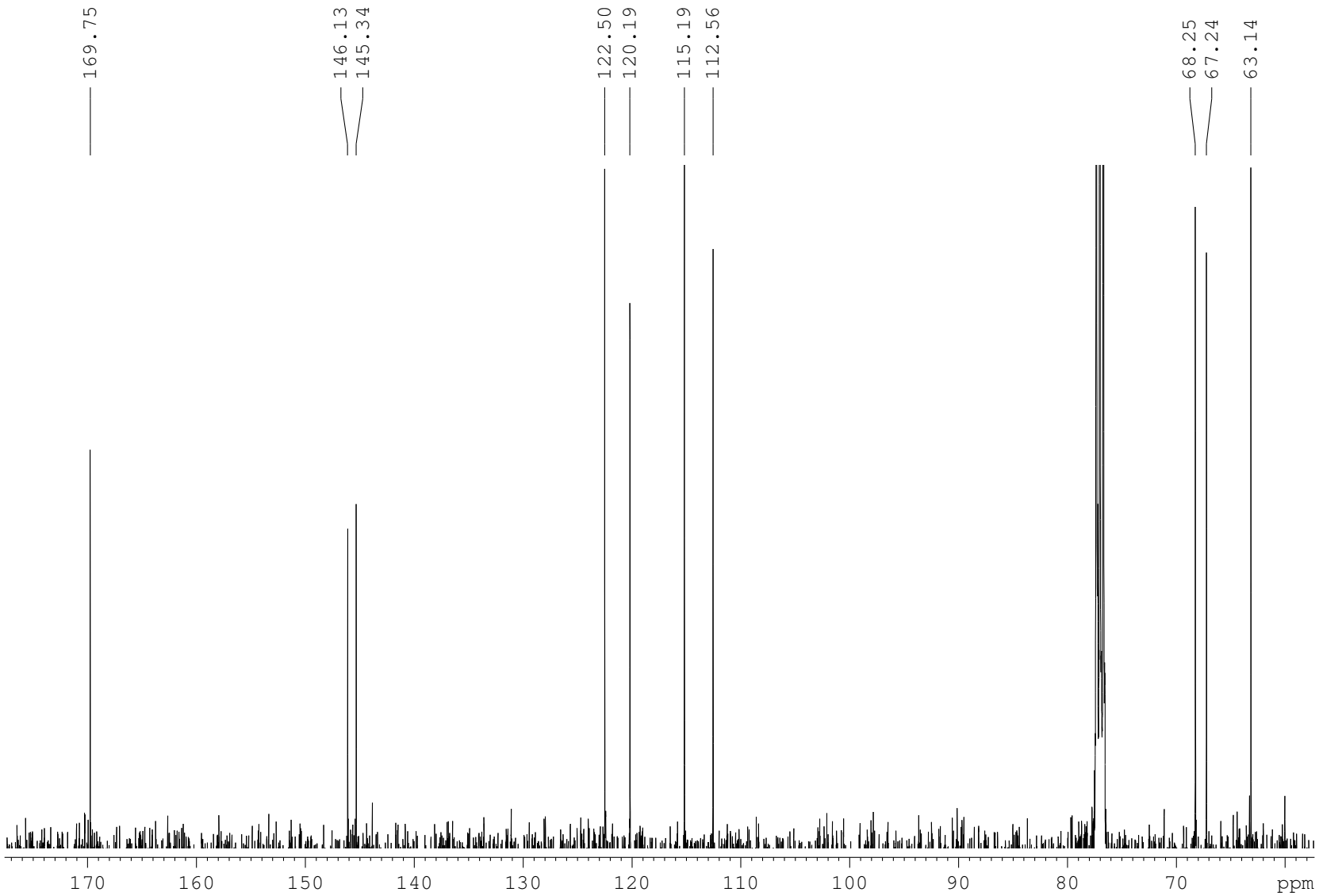

170.91
150.11
139.63
127.33
122.44
121.18
113.60
70.29
61.03
50.45
23.19
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

Compound: **344**

Bis(2-(2-Hydroxyethoxy)phenyl)diglycolate

^{1}H and ^{13}C NMR

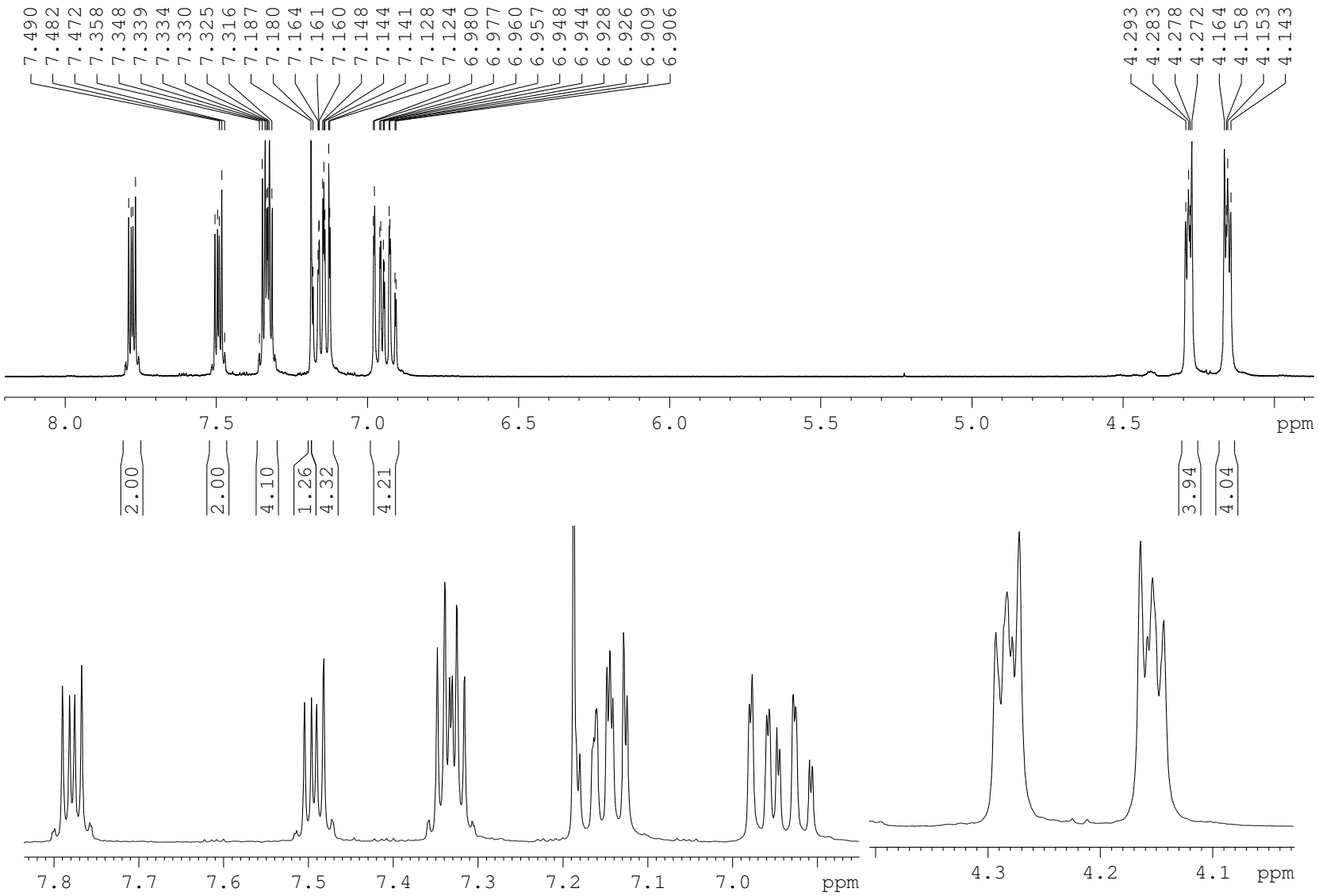

6.880
6.865
6.861
6.852
6.845
6.838
6.831
6.826
6.817
6.811
6.799
6.794
6.787
6.774
6.770
6.768
6.759
6.755
6.750
6.739
6.735
4.488
4.477
4.473
4.466
4.210
4.205
4.200
4.197
4.193
4.191
4.188
4.182
6.90
6.85
6.80
6.75
ppm
4.4
4.3
ppm
7.0
6.5
6.0
5.5
5.0
4.5
ppm
8.15
4.00
3.83
4.26

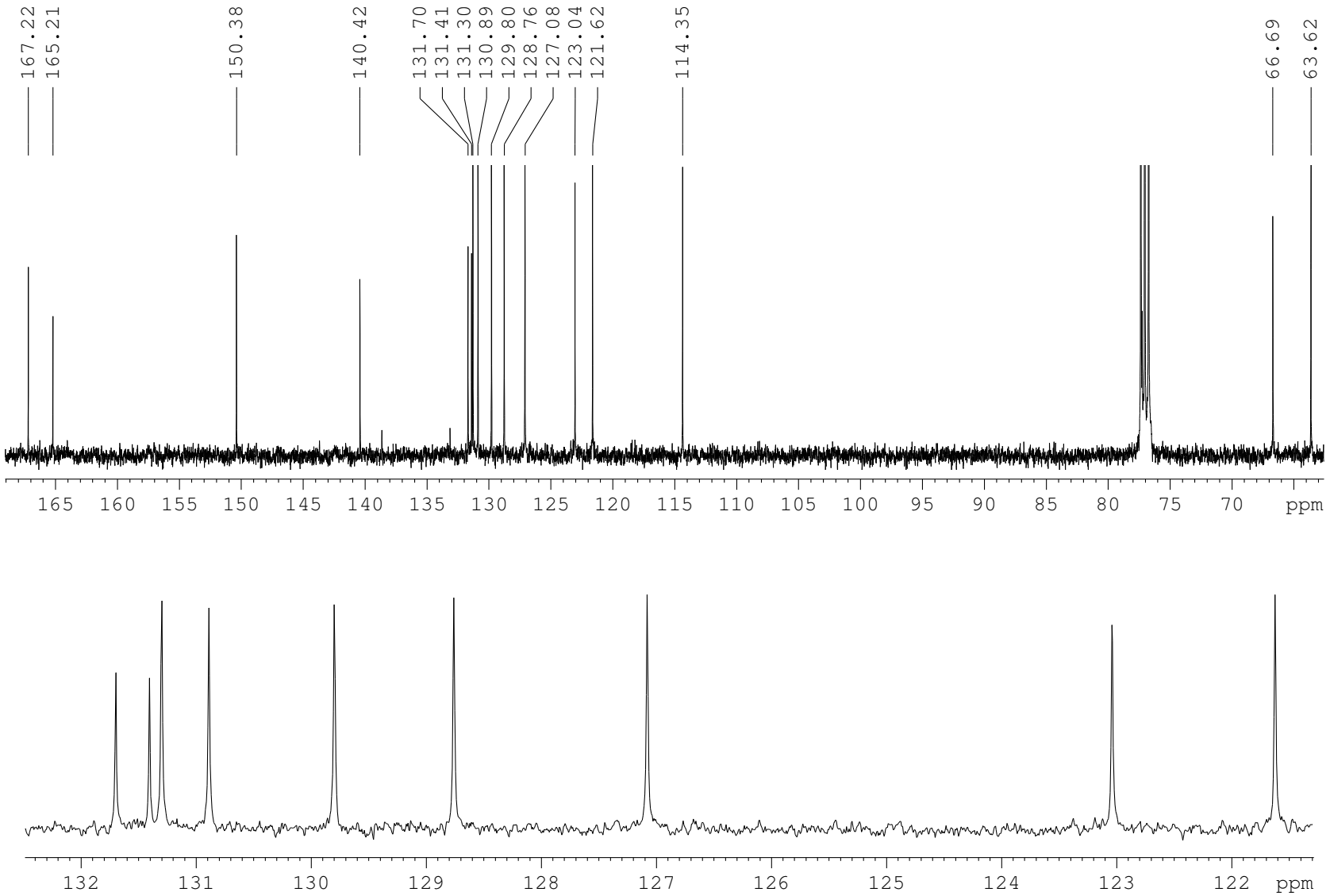

169.75
146.13
145.34
122.50
120.19
115.19
112.56
68.25
67.24
63.14
170
160
150
140
130
120
110
100
90
80
70
ppm

Compound: **348**

2,3,6,7,10,11,17,18-tetrabenzo-1,4,9,12,15,20-hexaoxacyclodoeicosa-2,6,10,17-tetraene-5,8,16,19-tetraone

^{1}H and ^{13}C NMR

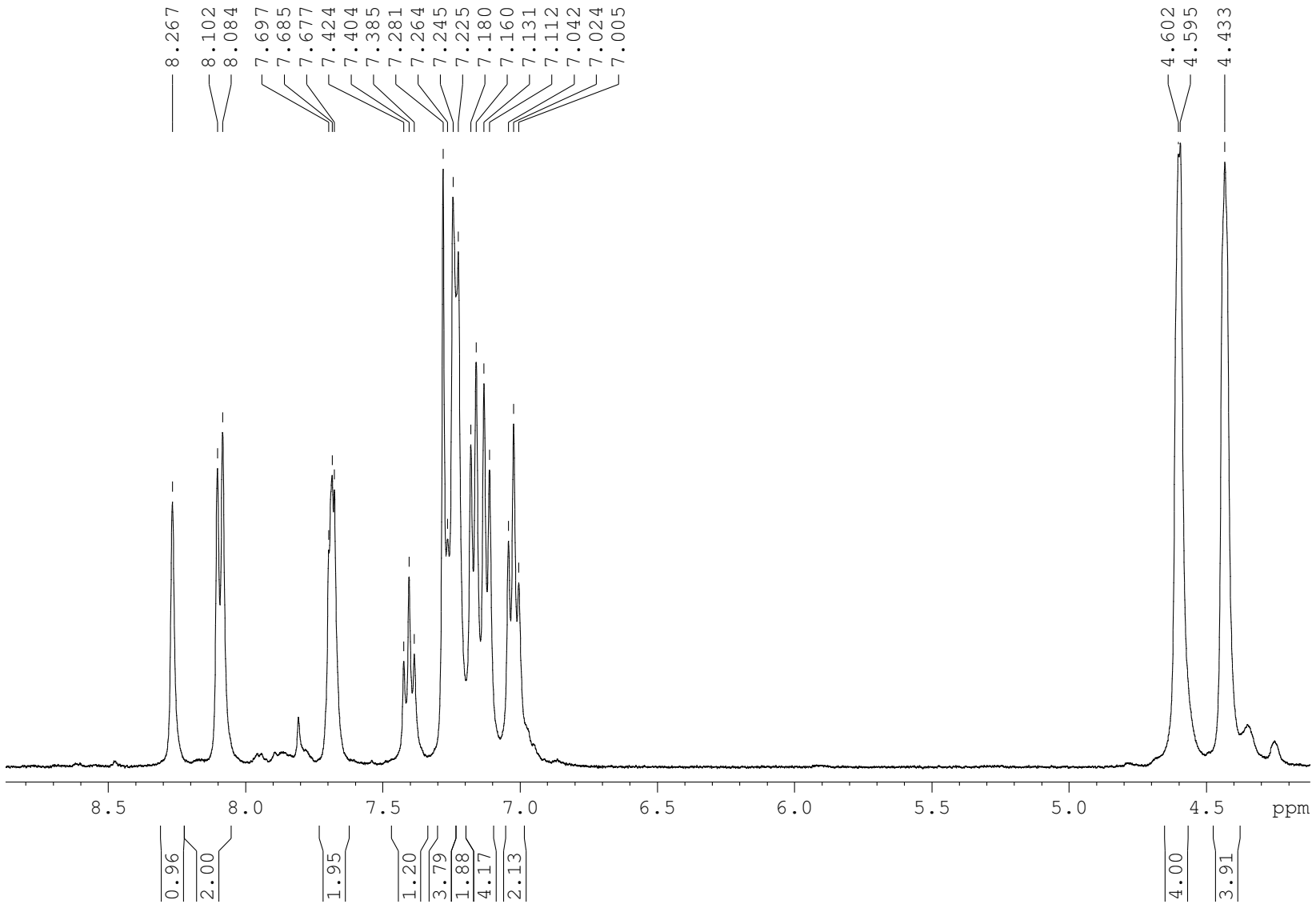

7.490
7.482
7.472
7.358
7.348
7.339
7.334
7.330
7.325
7.316
7.187
7.180
7.164
7.161
7.160
7.148
7.144
7.141
7.128
7.124
6.980
6.977
6.960
6.957
6.948
6.944
6.928
6.926
6.909
6.906
4.293
4.283
4.278
4.272
4.164
4.158
4.153
4.143
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm
2.00
2.00
4.10
1.26
4.32
4.21
3.94
4.04
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
ppm
4.3
4.2
4.1
ppm

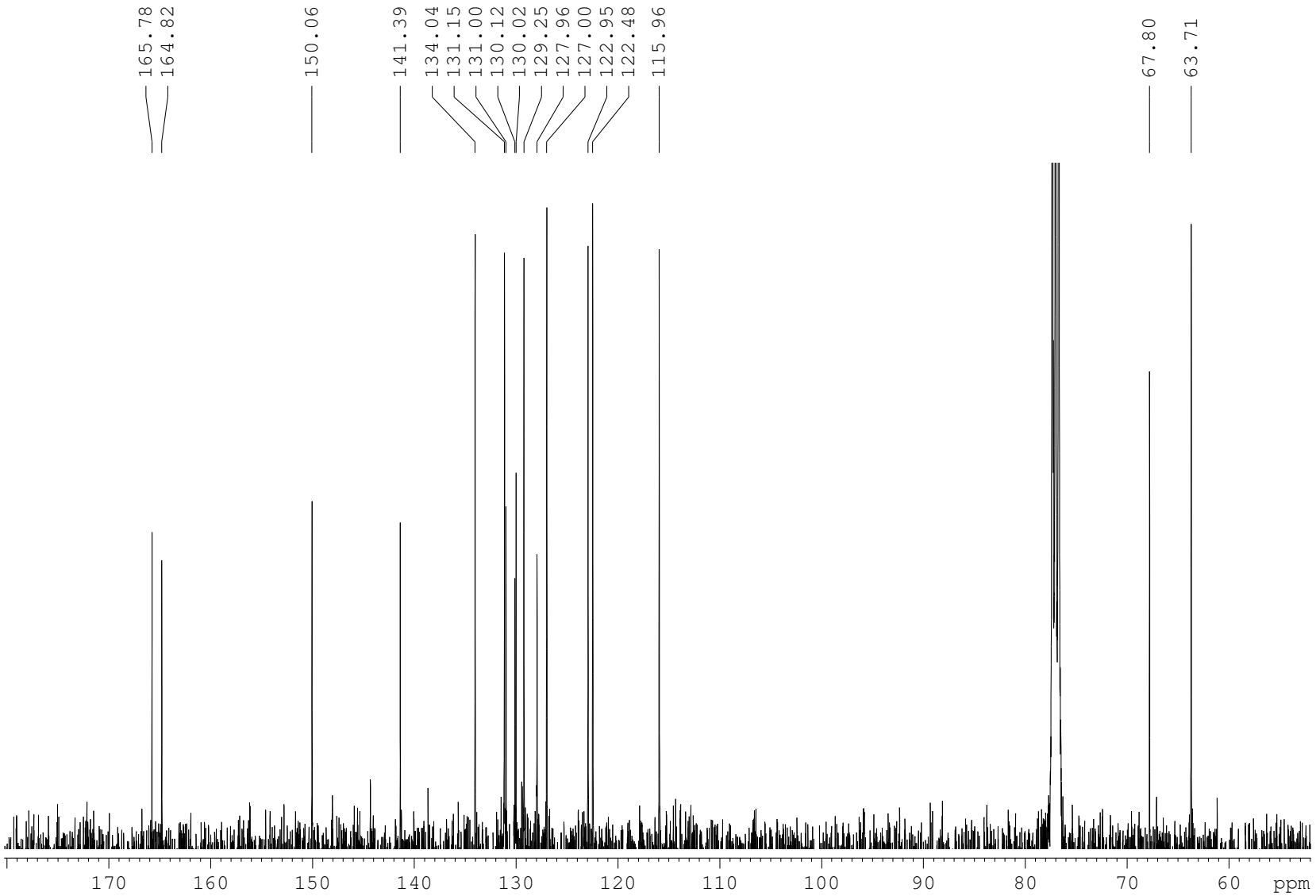

167.22
165.21
150.38
140.42
131.70
131.41
131.30
130.89
129.80
128.76
127.08
123.04
121.62
114.35
66.69
63.62
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 ppm
132 131 130 129 128 127 126 125 124 123 122 ppm

Compound: **349**

2,3,6,7,10,11,17,19-tetrabenzo-1,4,9,12,15,21-hexaoxacyclotrieicosa-2,6,10,17-tetraene-5,8,16,20-tetraone

^{1}H and ^{13}C NMR

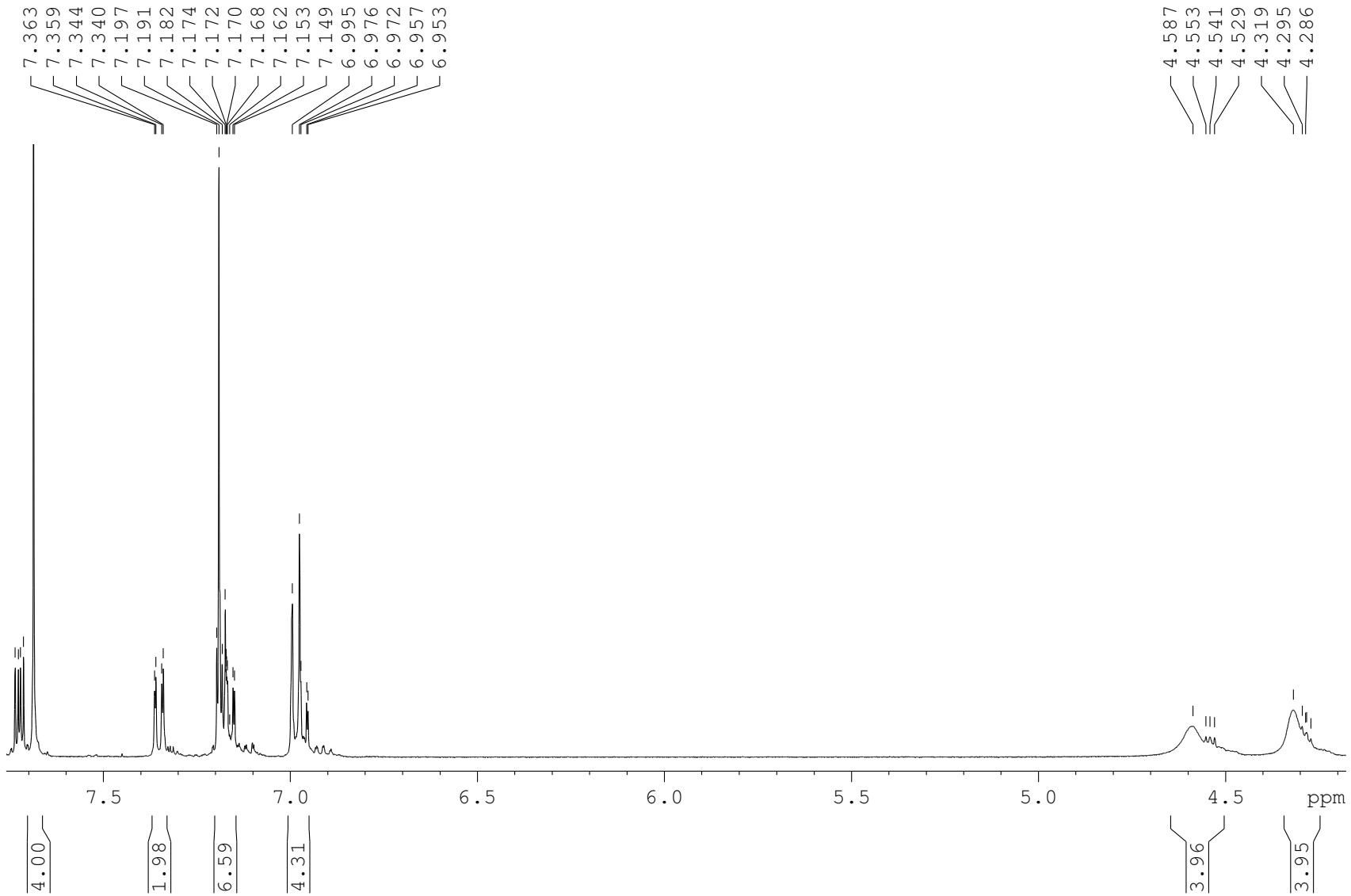

8.267
8.102
8.084
7.697
7.685
7.677
7.424
7.404
7.385
7.281
7.264
7.245
7.225
7.180
7.160
7.131
7.112
7.042
7.024
7.005
4.602
4.595
4.433
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm
0.96
2.00
1.95
1.20
3.79
1.88
4.17
2.13
4.00
3.91

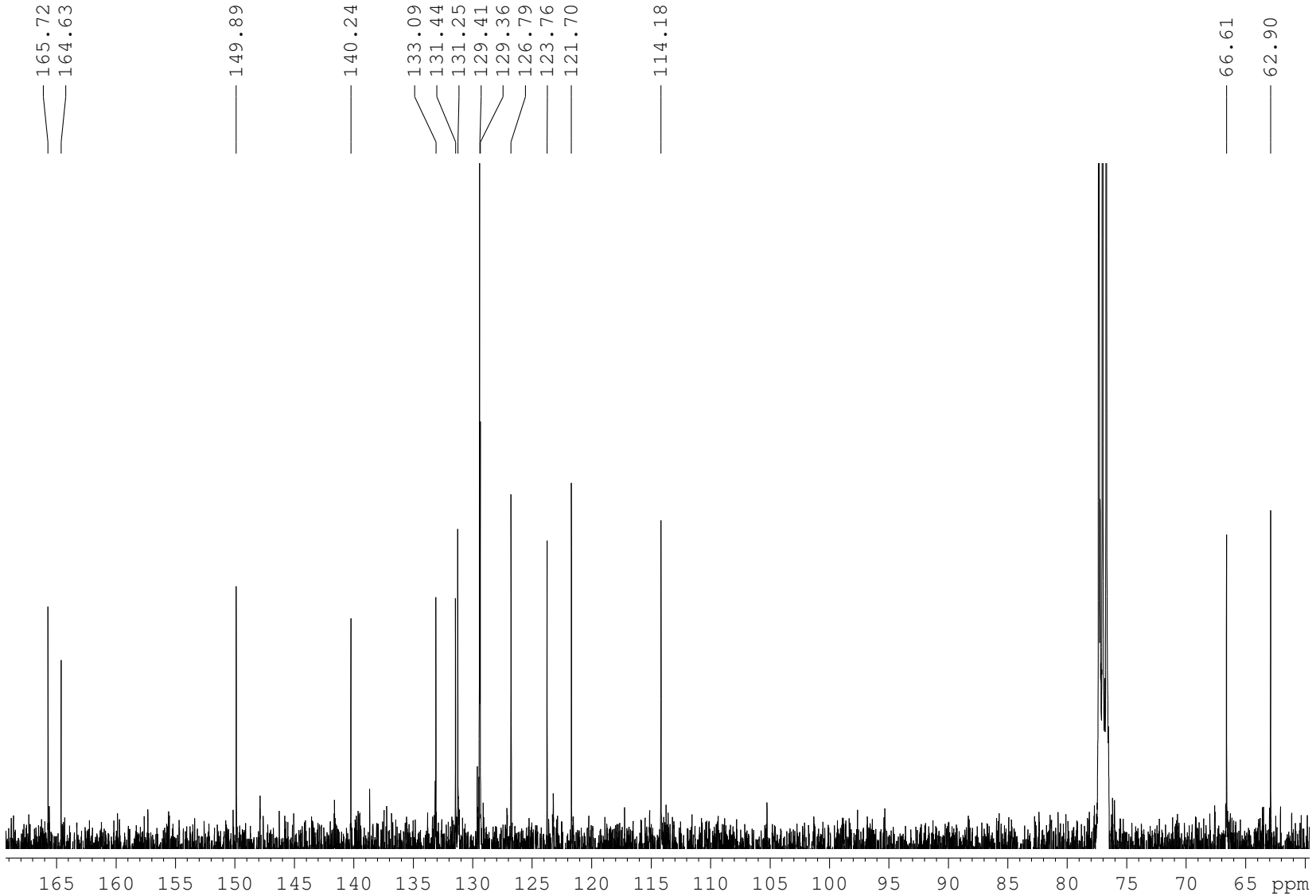

165.78
164.82
150.06
141.39
134.04
131.15
131.00
130.12
130.02
129.25
127.96
127.00
122.95
122.48
115.96
67.80
63.71
170
160
150
140
130
120
110
100
90
80
70
60
ppm

Compound: **350**

2,3,6,7,10,11,17,20-tetrabenzo-1,4,9,12,15,22-hexaoxacyclotetraeicosa-2,6,10,17,19-pentaene-5,8,16,21-tetraone

^{1}H and ^{13}C NMR

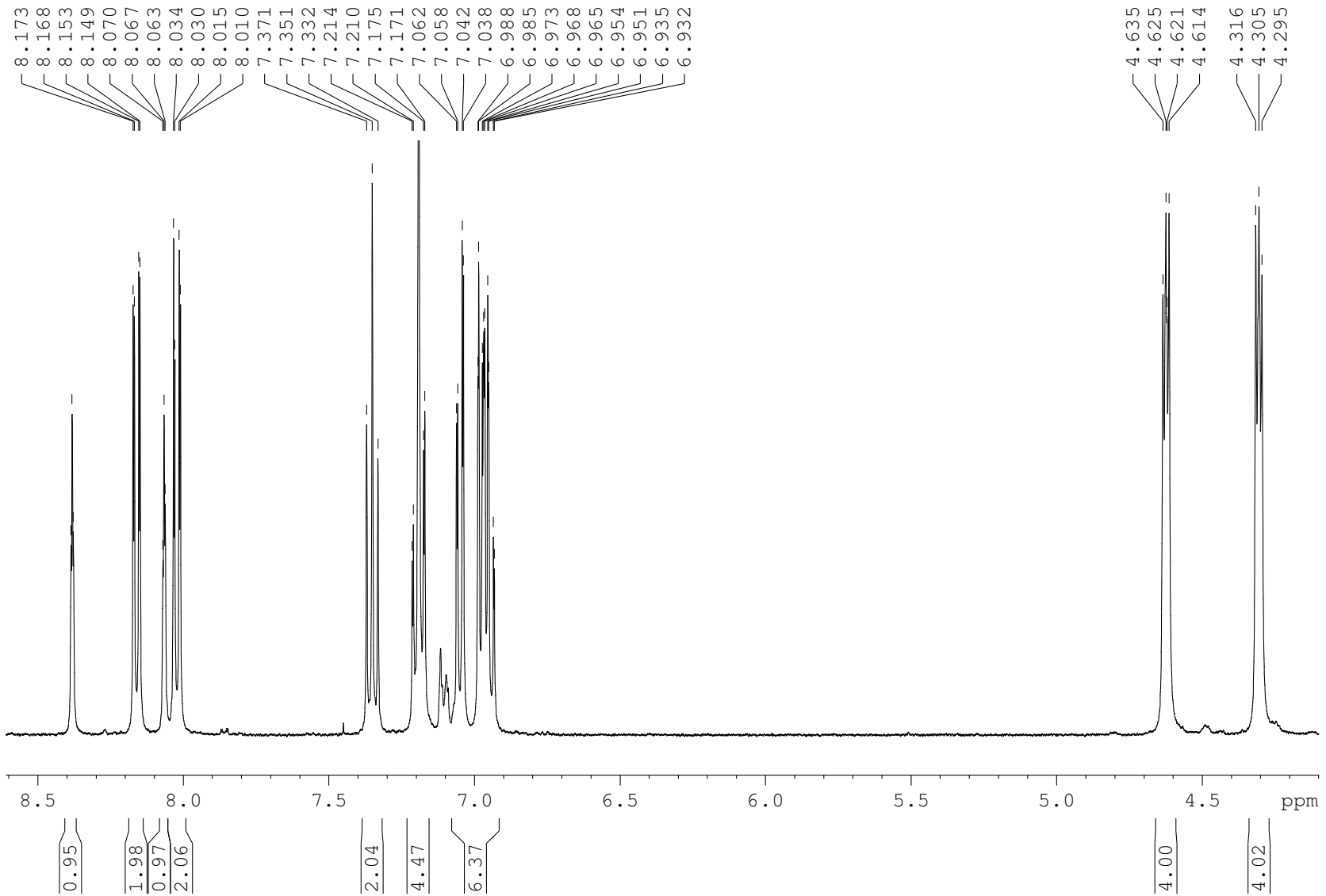

7.363
7.359
7.344
7.340
7.197
7.191
7.182
7.174
7.172
7.170
7.168
7.162
7.153
7.149
6.995
6.976
6.972
6.957
6.953
4.587
4.553
4.541
4.529
4.319
4.295
4.286
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm
4.00
1.98
6.59
4.31
3.96
3.95

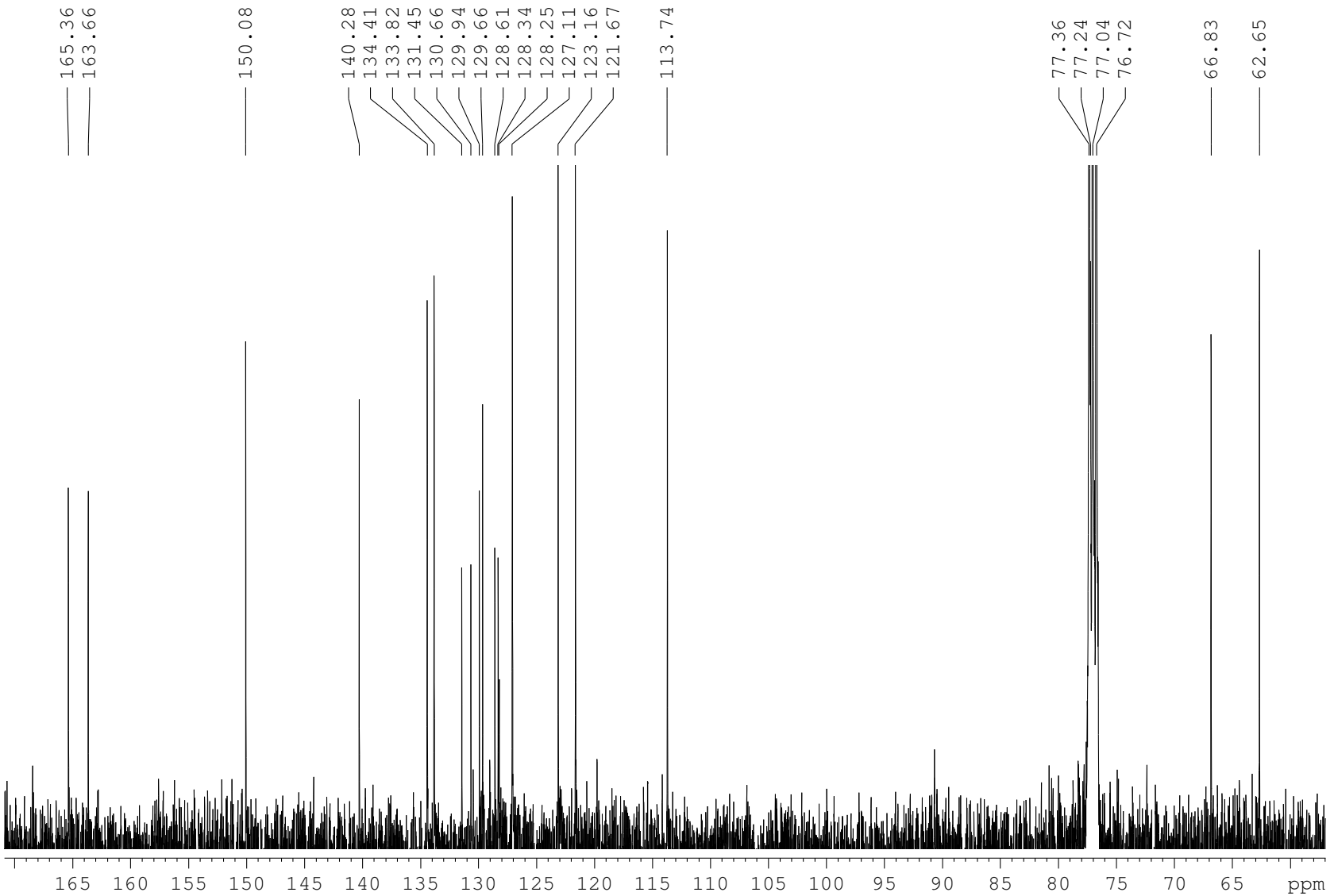

165.72
164.63
149.89
140.24
133.09
131.44
131.25
129.41
129.36
126.79
123.76
121.70
114.18
66.61
62.90
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 ppm

Compound: **351**

2,3,6,8,11,12,18,20-tetrabenzo-1,4,10,13,16,22-hexaoxacyclotetraeicosa-2,6,11,18-tetraene-5,9,17,21-tetraone

^{1}H and ^{13}C NMR

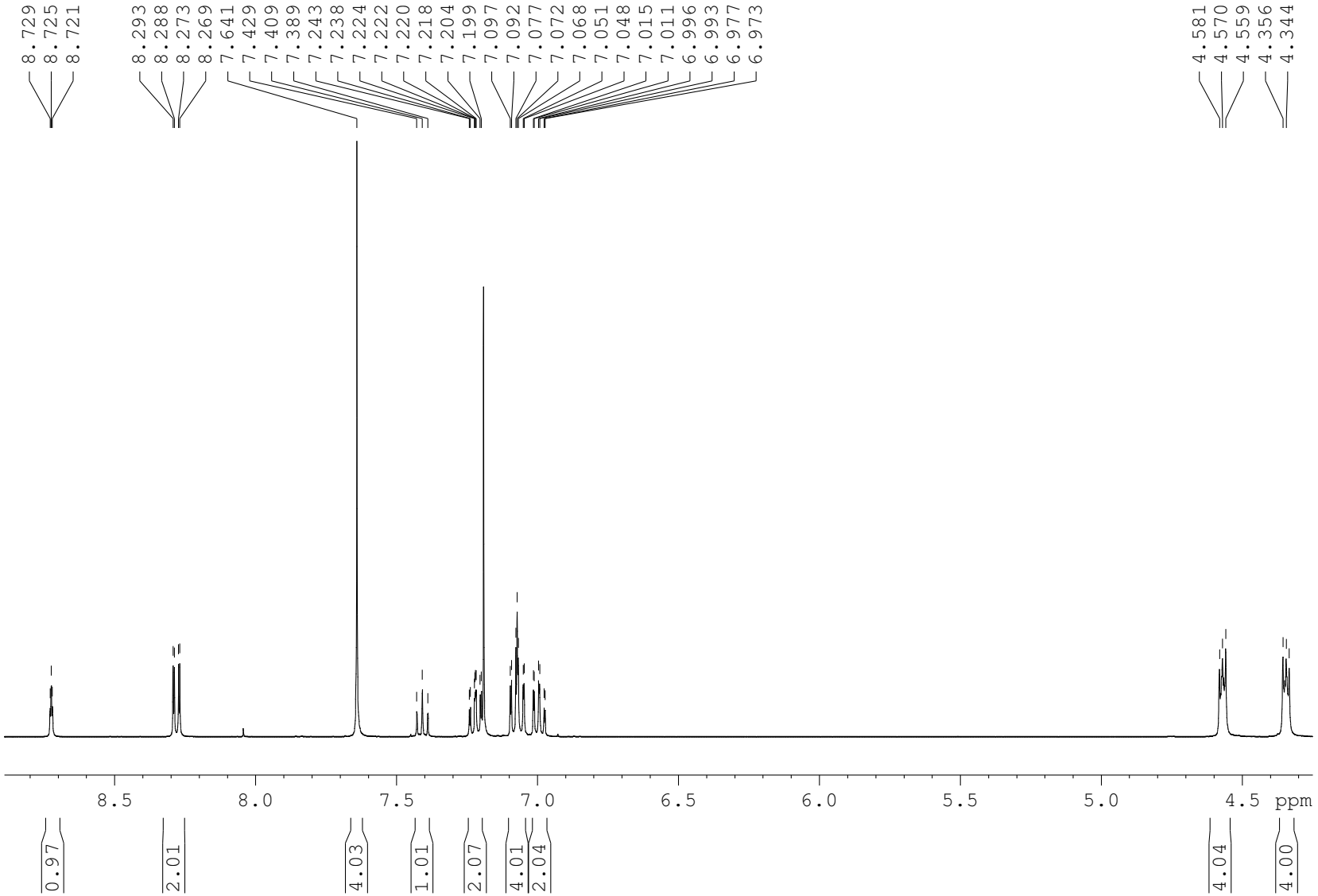

8.173
8.168
8.153
8.149
8.070
8.067
8.063
8.034
8.030
8.015
8.010
7.371
7.351
7.332
7.214
7.210
7.175
7.171
7.062
7.058
7.042
7.038
6.988
6.985
6.973
6.968
6.965
6.954
6.951
6.935
6.932
4.635
4.625
4.621
4.614
4.316
4.305
4.295
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm
0.95
1.98
0.97
2.06
2.04
4.47
6.37
4.00
4.02

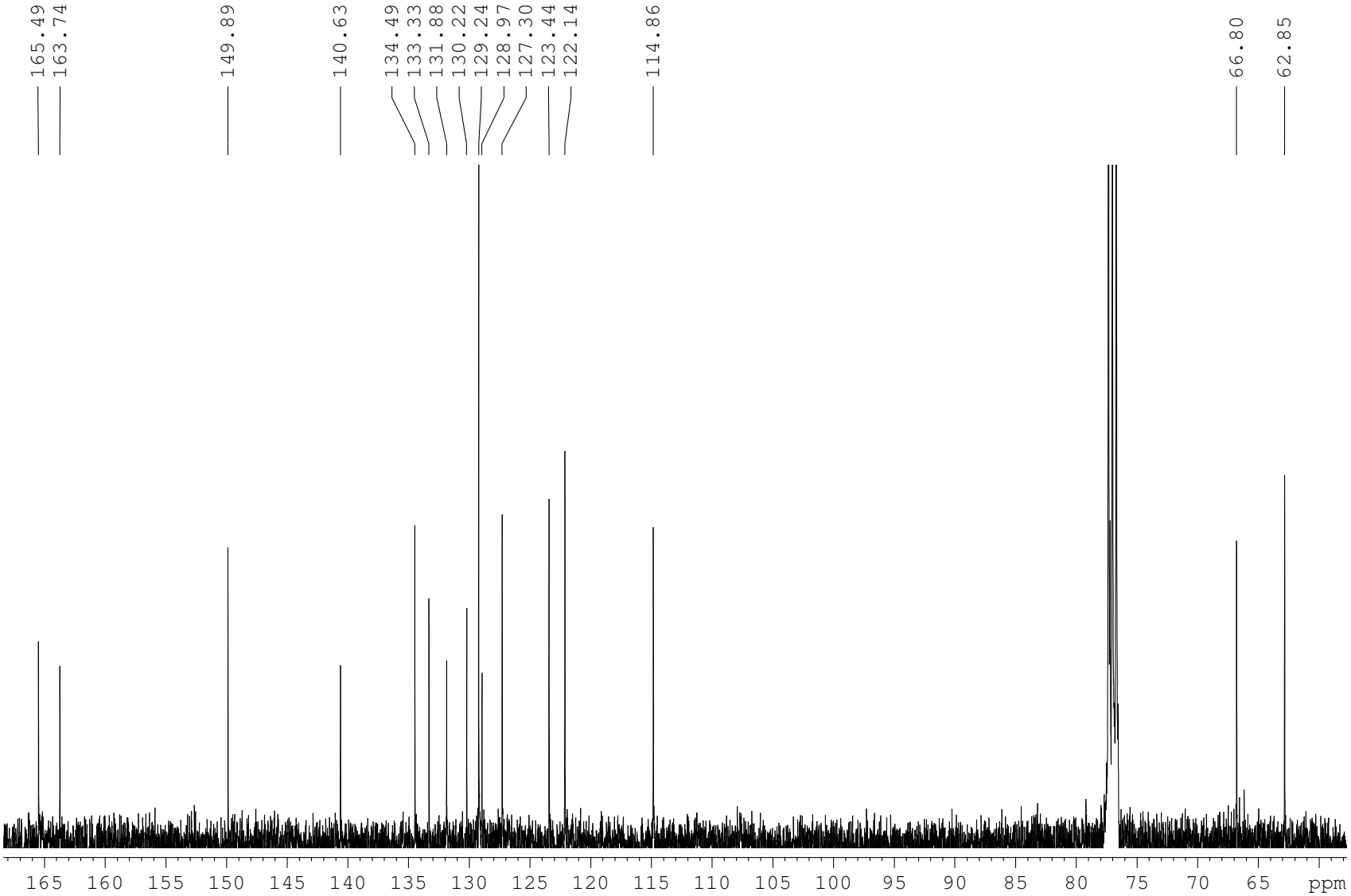

165.36
163.66
150.08
140.28
134.41
133.82
131.45
130.66
129.94
129.66
128.61
128.34
128.25
127.11
123.16
121.67
113.74
77.36
77.24
77.04
76.72
66.83
62.65
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 ppm

Compound: **352**

2,3,6,8,11,12,18,21-tetrabenzo-1,4,10,13,16,23-hexaoxacyclopentaeicosa-2,6,11,18,20-pentaene-5,9,17,22-tetraone

^{1}H and ^{13}C NMR

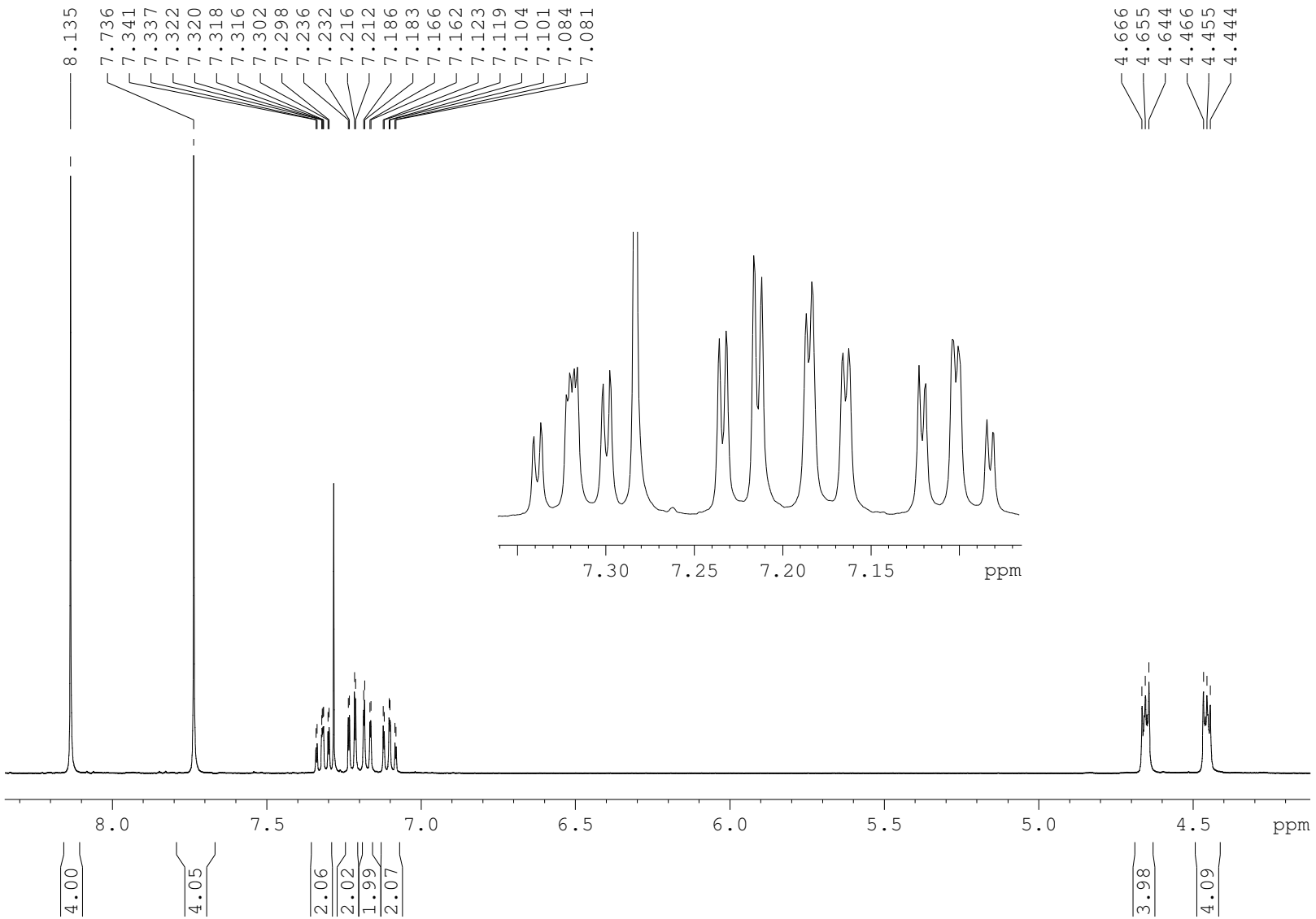

8.729
8.725
8.721
8.293
8.288
8.273
8.269
7.641
7.429
7.409
7.389
7.243
7.238
7.224
7.222
7.220
7.218
7.204
7.199
7.097
7.092
7.077
7.072
7.068
7.051
7.048
7.015
7.011
6.996
6.993
6.977
6.973
4.581
4.570
4.559
4.356
4.344
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm
0.97
2.01
4.03
1.01
2.07
4.01
2.04
4.04
4.00

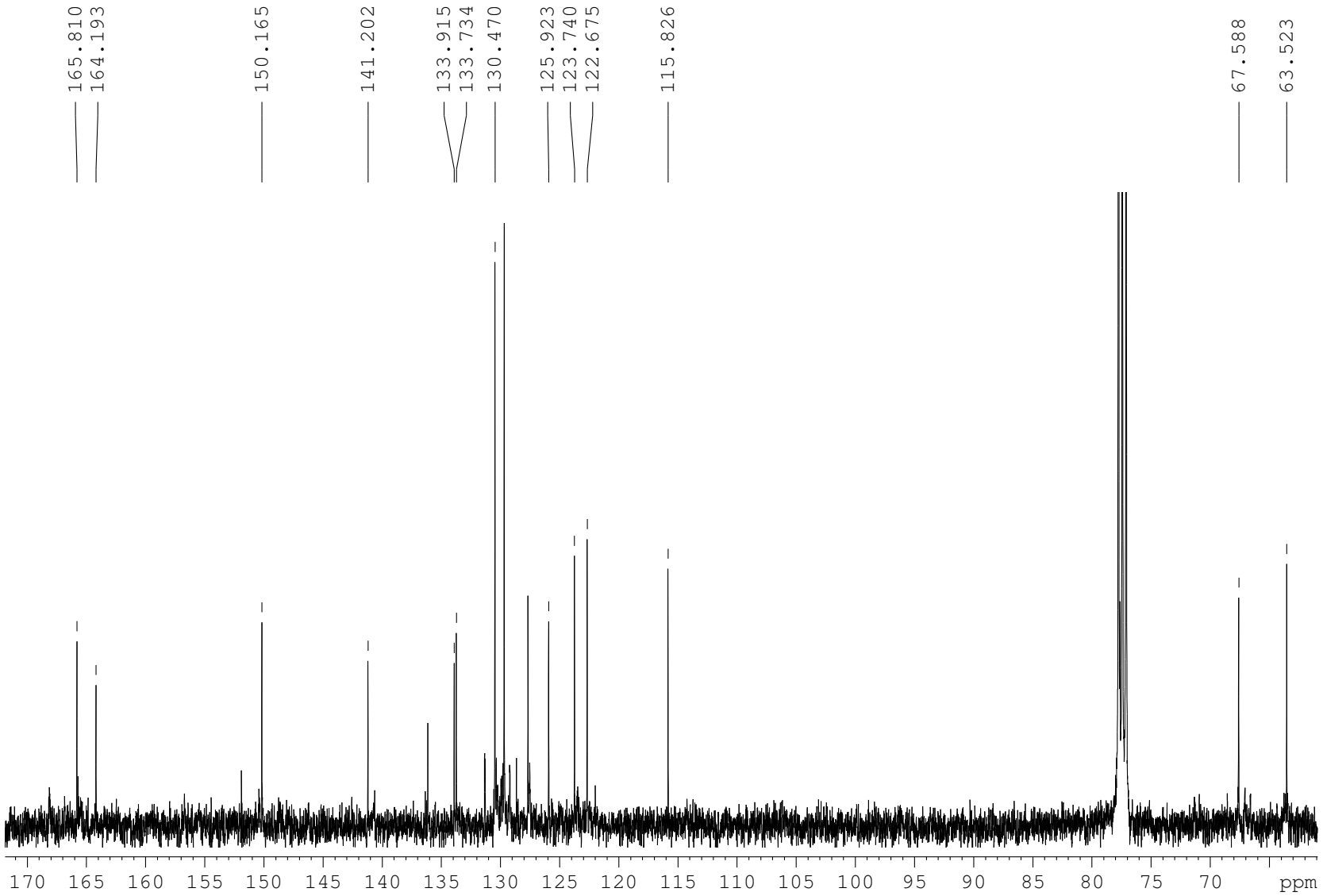

165.49
163.74
149.89
140.63
134.49
133.33
131.88
130.22
129.24
128.97
127.30
123.44
122.14
114.86
66.80
62.85
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 ppm

Compound: **353**

2,3,6,9,11,12,13,19,22-tetrabenzo-1,4,11,14,17,24-hexaoxacyclohexaeicosa-2,6,8,12,19,21-hexaene-5,10,18,23-tetraone

^{1}H and ^{13}C NMR

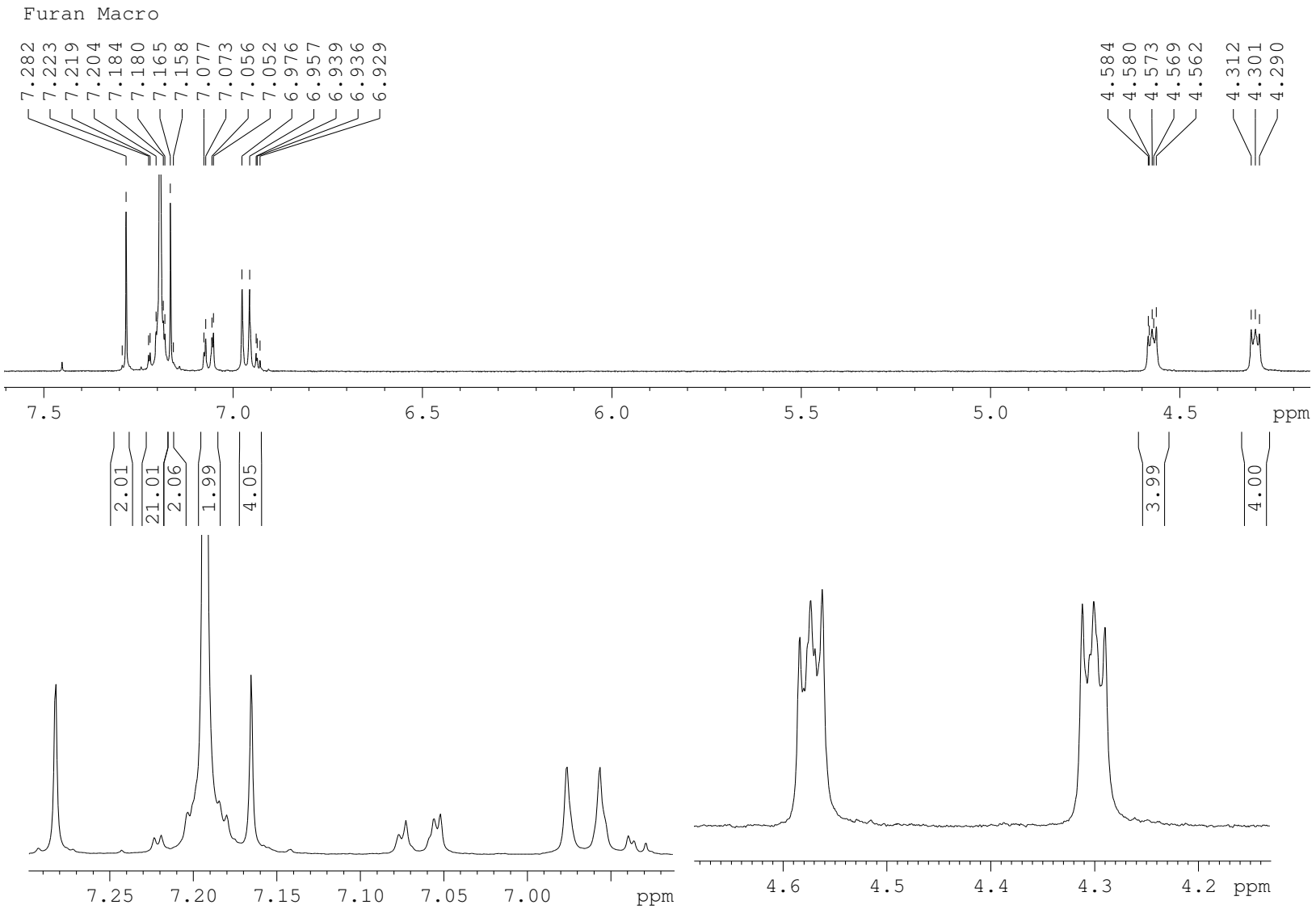

8.135
7.736
7.341
7.337
7.322
7.320
7.318
7.316
7.302
7.298
7.236
7.232
7.216
7.212
7.186
7.183
7.166
7.162
7.123
7.119
7.104
7.101
7.084
7.081
4.666
4.655
4.644
4.466
4.455
4.444
7.30
7.25
7.20
7.15
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm
4.00
4.05
2.06
2.02
1.99
2.07
3.98
4.09

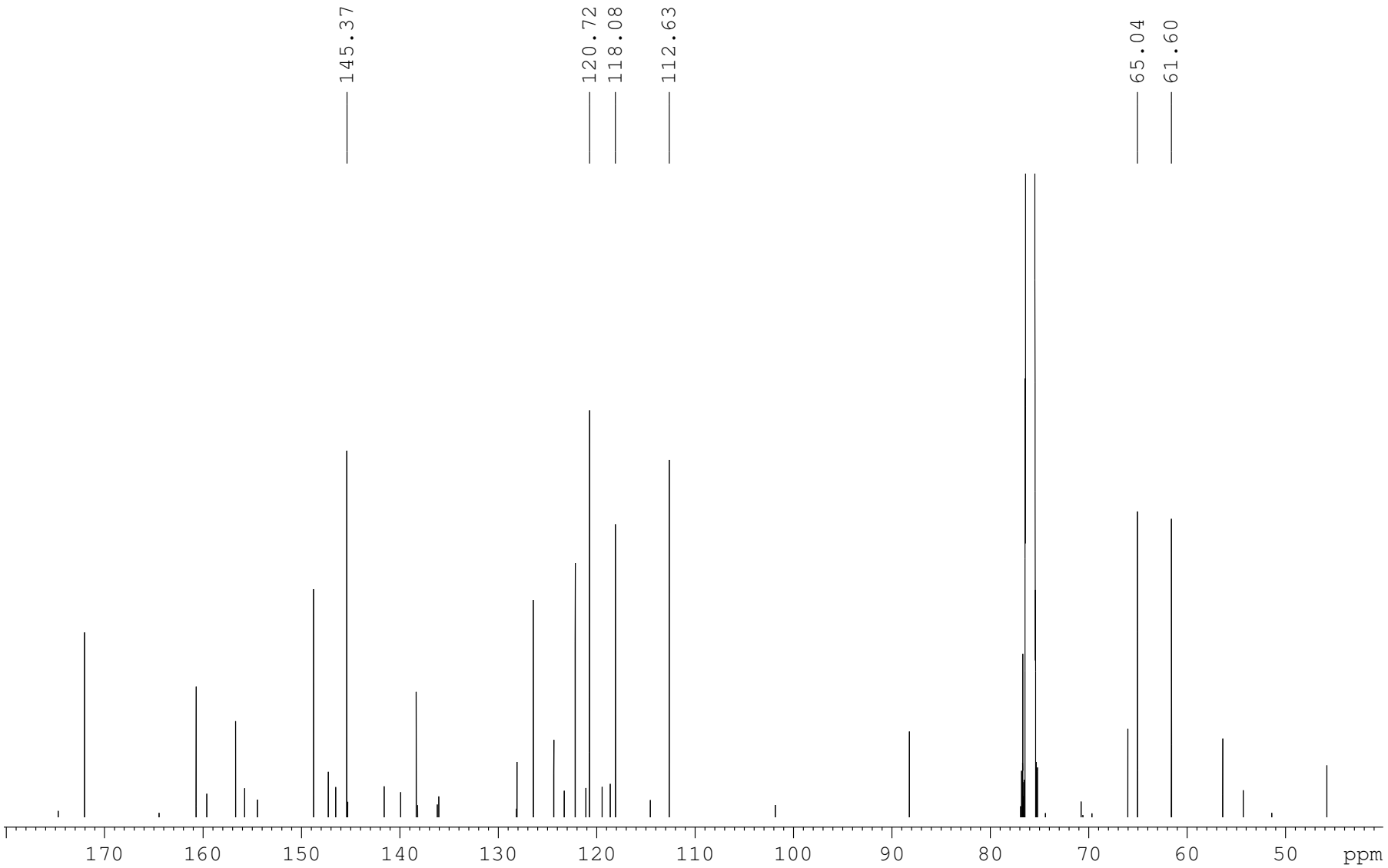

165.810
164.193
150.165
141.202
133.915
133.734
130.470
125.923
123.740
122.675
115.826
67.588
63.523
170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70
ppm

Compound: **354**

2,3,11,12,-dibenzo-6,8,18,20-difurano-1,4,7,10,13,16,19,22-octaoxacyclohexaeicosa-2,11-diaene-5,9,17,21-tetraone

^{1}H and ^{13}C NMR


Furan Macro
7.282
7.223
7.219
7.204
7.184
7.180
7.165
7.158
7.077
7.073
7.056
7.052
6.976
6.957
6.939
6.936
6.929
4.584
4.580
4.573
4.569
4.562
4.312
4.301
4.290
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm
2.01
21.01
2.06
1.99
4.05
3.99
4.00
7.25
7.20
7.15
7.10
7.05
7.00
ppm
4.6
4.5
4.4
4.3
4.2
ppm

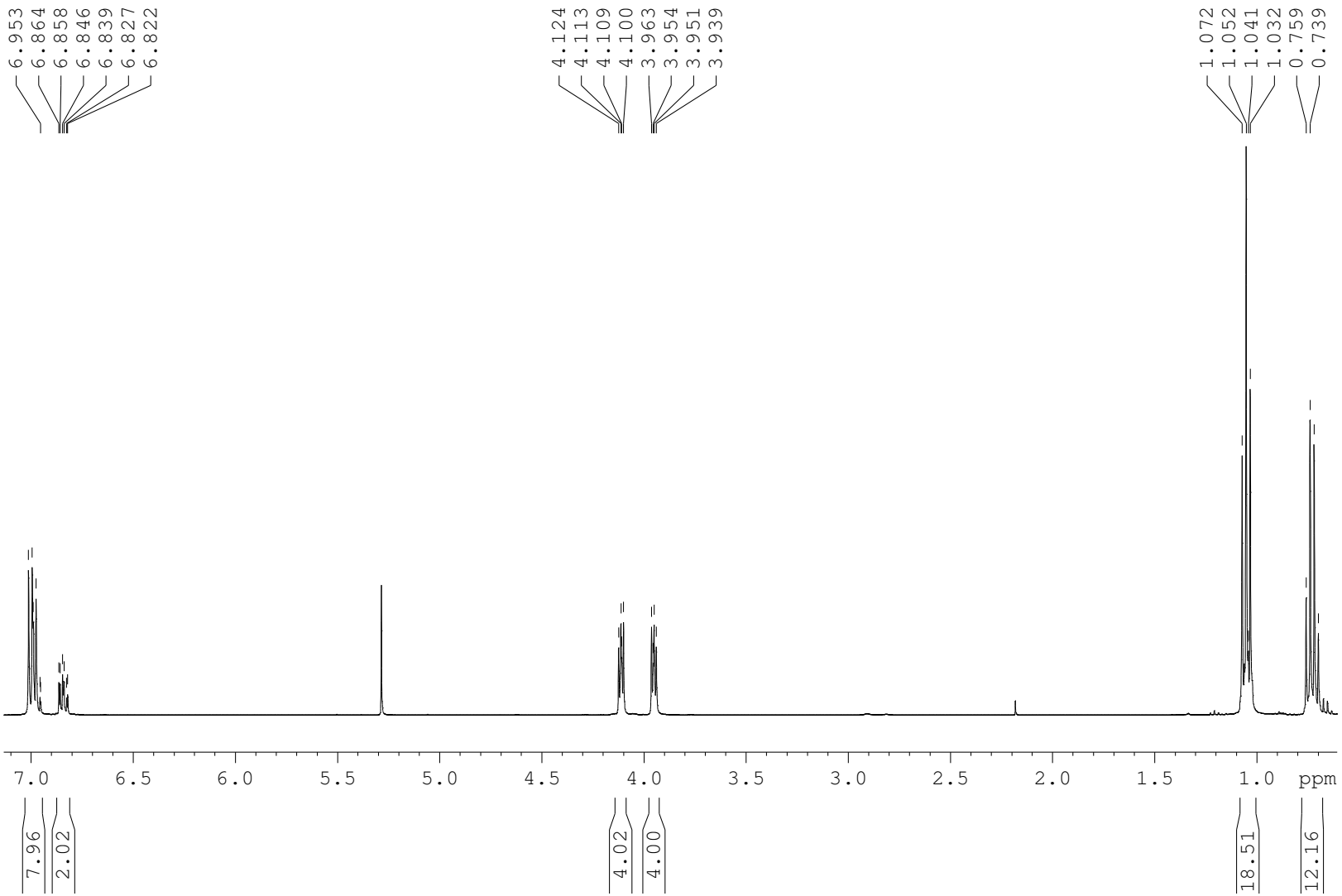

145.37
120.72
118.08
112.63
65.04
61.60
170
160
150
140
130
120
110
100
90
80
70
60
50
ppm

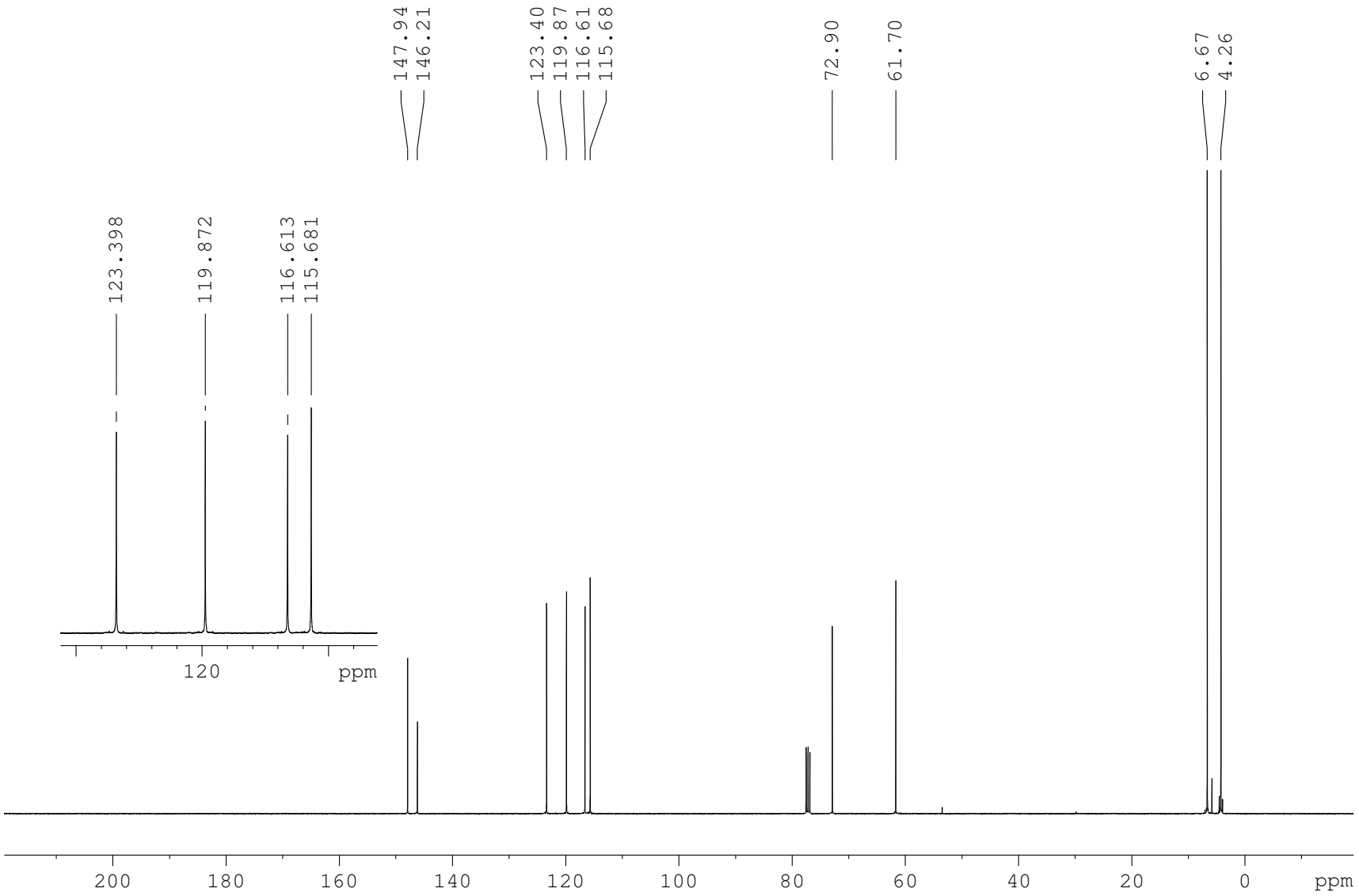
Compound: **345**

2-(2-(Triethylsilyloxy)phenoxy)ethanol

^{1}H and ^{13}C NMR

TES protected Diol

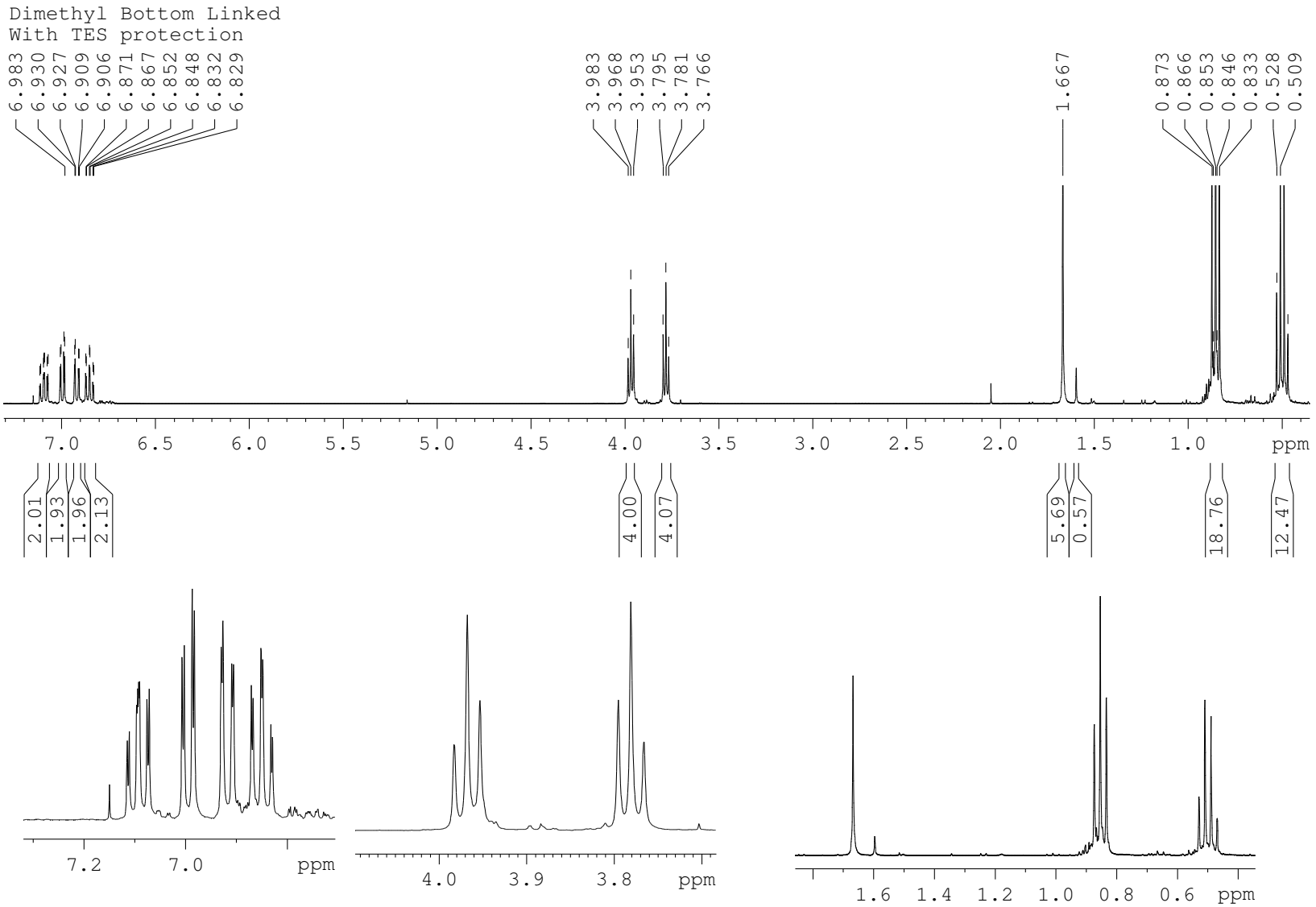


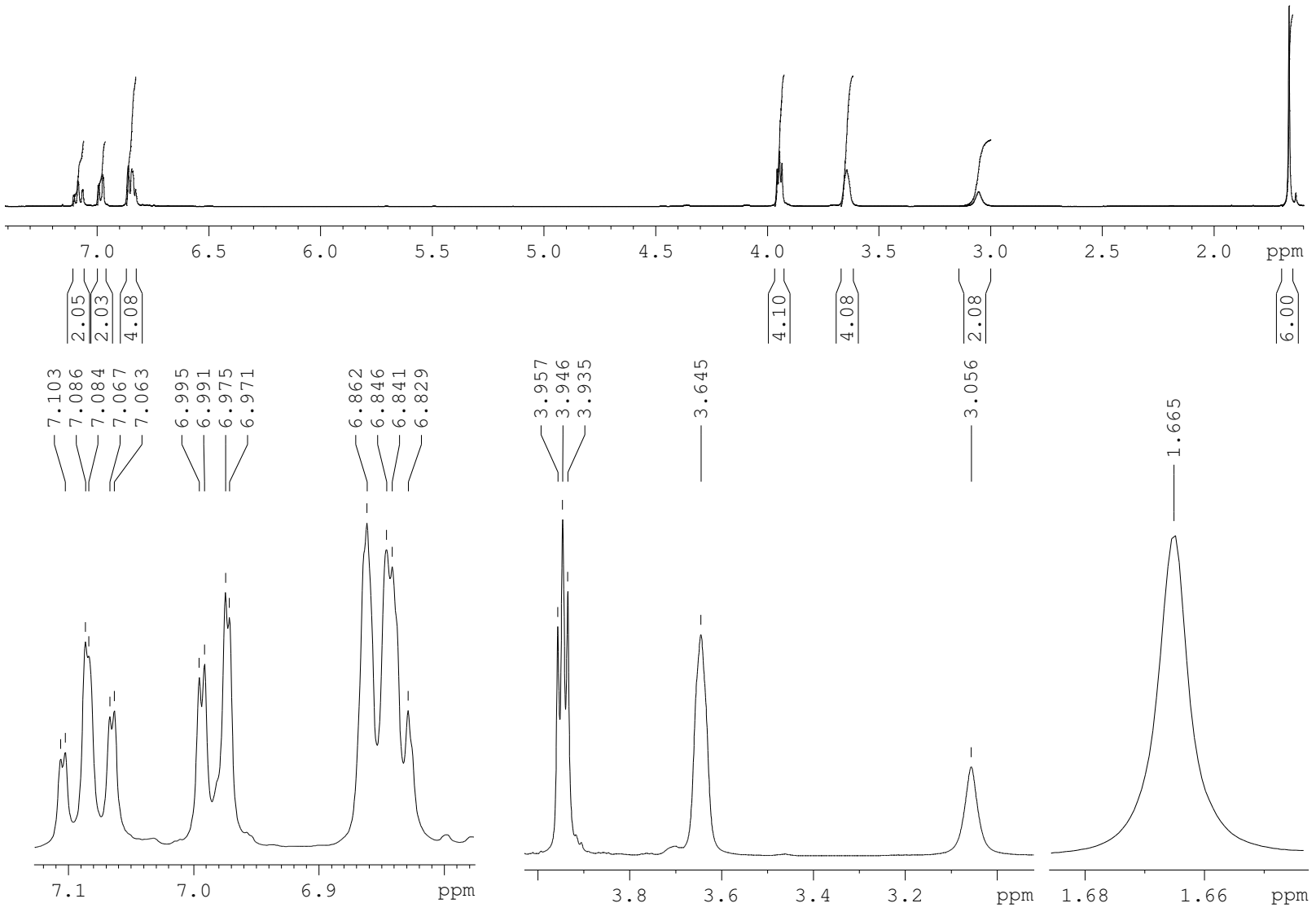

147.94
146.21
123.40
119.87
116.61
115.68
72.90
61.70
6.67
4.26
123.398
119.872
116.613
115.681
120
ppm
200
180
160
140
120
100
80
60
40
20
0
ppm

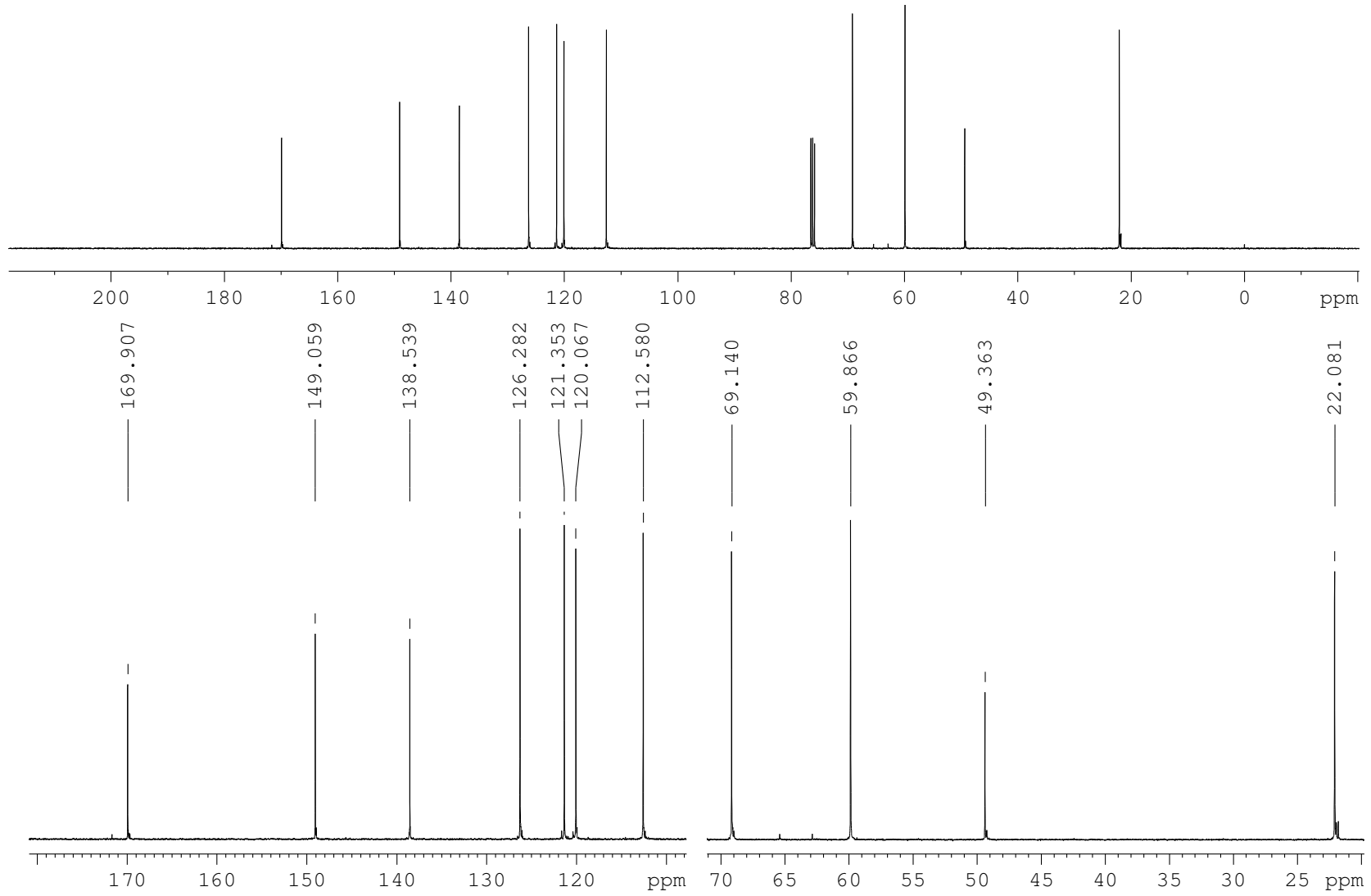
Compound: **346**

Bis(2-(2-Hydroxyphenoxy)ethyl)-2,2-dimethylmalonate

^{1}H and ^{13}C NMR


Dimethyl Bottom Linked
With TES protection
6.983
6.930
6.927
6.909
6.906
6.871
6.867
6.852
6.848
6.832
6.829
3.983
3.968
3.953
3.795
3.781
3.766
1.667
0.873
0.866
0.853
0.846
0.833
0.528
0.509
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.01
1.93
1.96
2.13
4.00
4.07
5.69
0.57
18.76
12.47
7.2
7.0
ppm
4.0
3.9
3.8
ppm
1.6
1.4
1.2
1.0
0.8
0.6
ppm

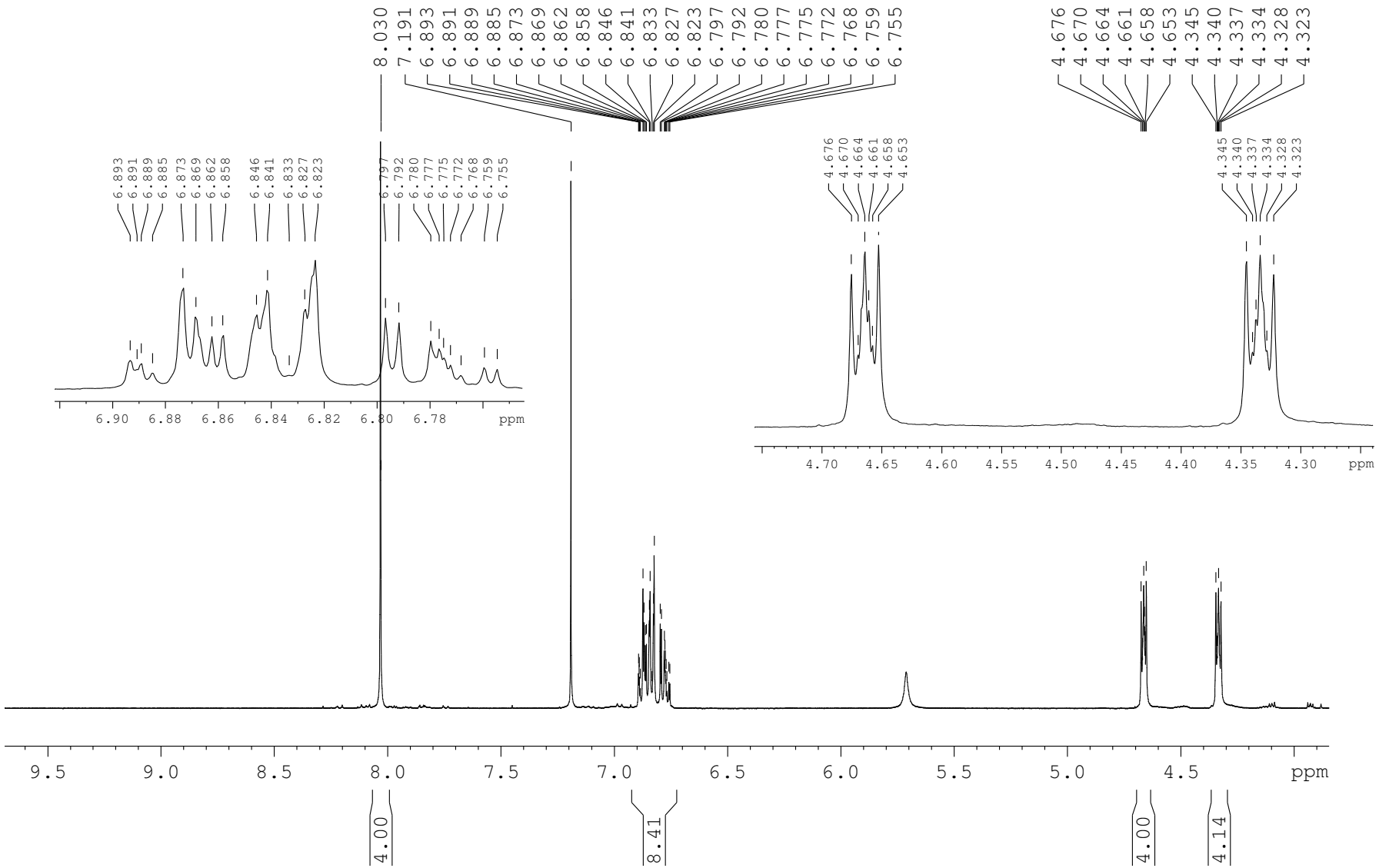

7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
2.05
2.03
4.08
4.10
4.08
2.08
6.00
7.103
7.086
7.084
7.067
7.063
6.995
6.991
6.975
6.971
6.862
6.846
6.841
6.829
3.957
3.946
3.935
3.645
3.056
1.665
7.1
7.0
6.9
ppm
3.8
3.6
3.4
3.2
ppm
1.68
1.66
ppm

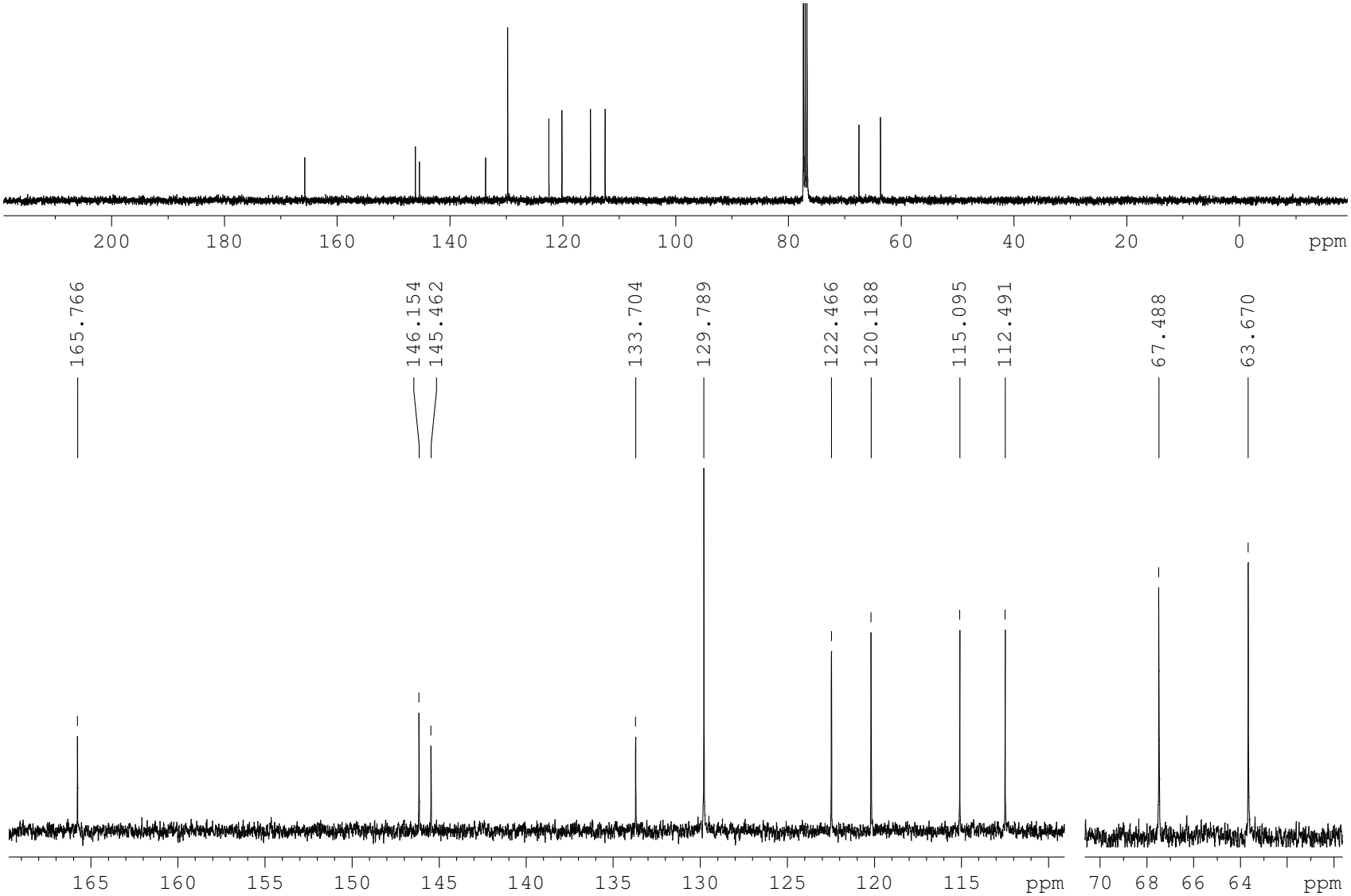

200
180
160
140
120
100
80
60
40
20
0
ppm
169.907
149.059
138.539
126.282
121.353
120.067
112.580
69.140
59.866
49.363
22.081
170
160
150
140
130
120
ppm
70
65
60
55
50
45
40
35
30
25
ppm

Compound: **347**

Bis(2-(2-Hydroxyphenoxy)ethyl)terephthalate

^{1}H and ^{13}C NMR

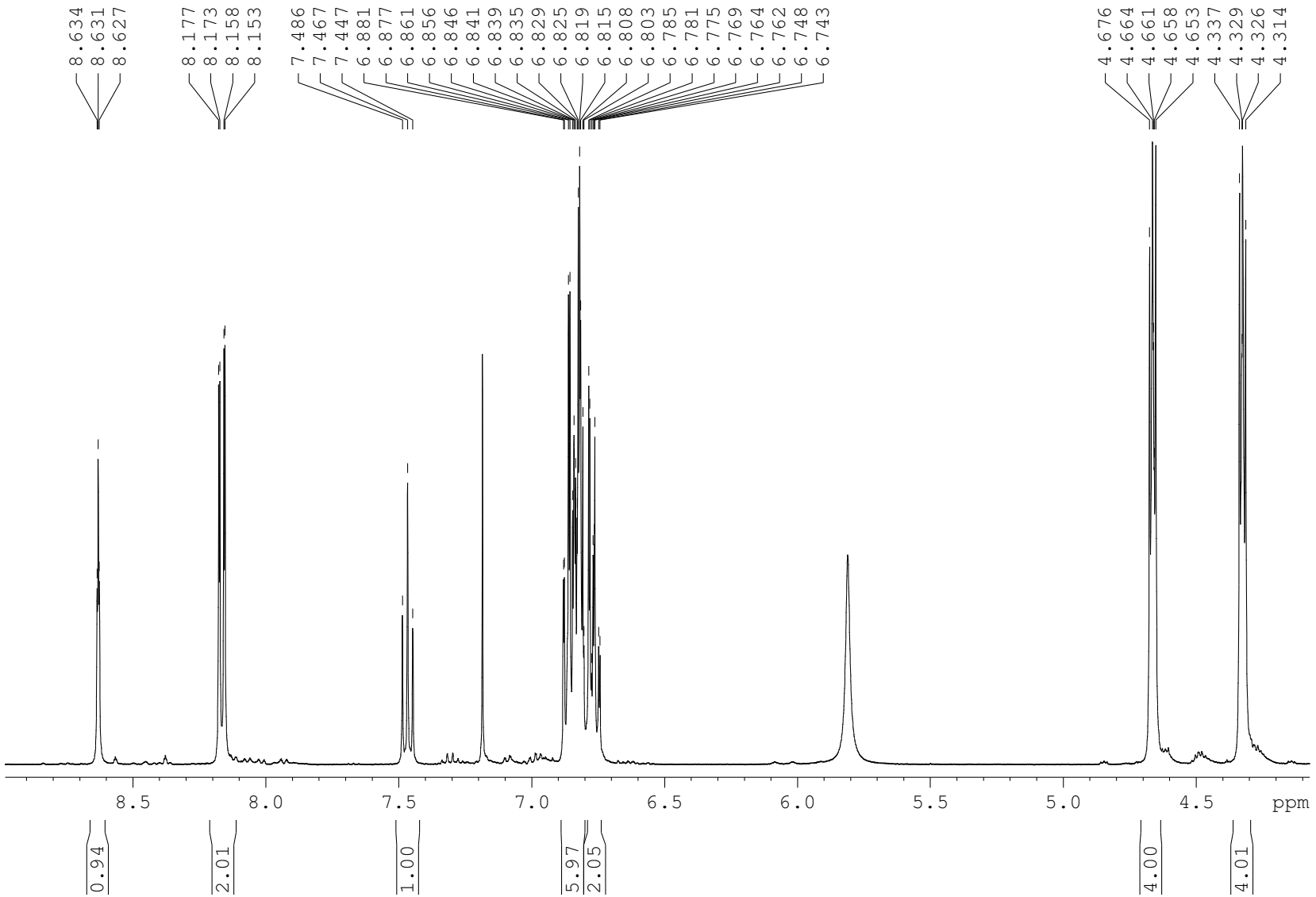

8.030
7.191
6.893
6.891
6.889
6.885
6.873
6.869
6.862
6.858
6.846
6.841
6.833
6.827
6.823
6.797
6.792
6.780
6.777
6.775
6.772
6.768
6.759
6.755
4.676
4.670
4.664
4.661
4.658
4.653
4.345
4.340
4.337
4.334
4.328
4.323
6.90 6.88 6.86 6.84 6.82 6.80 6.78 ppm
4.70 4.65 4.60 4.55 4.50 4.45 4.40 4.35 4.30 ppm
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 ppm
4.00
8.41
4.00
4.14

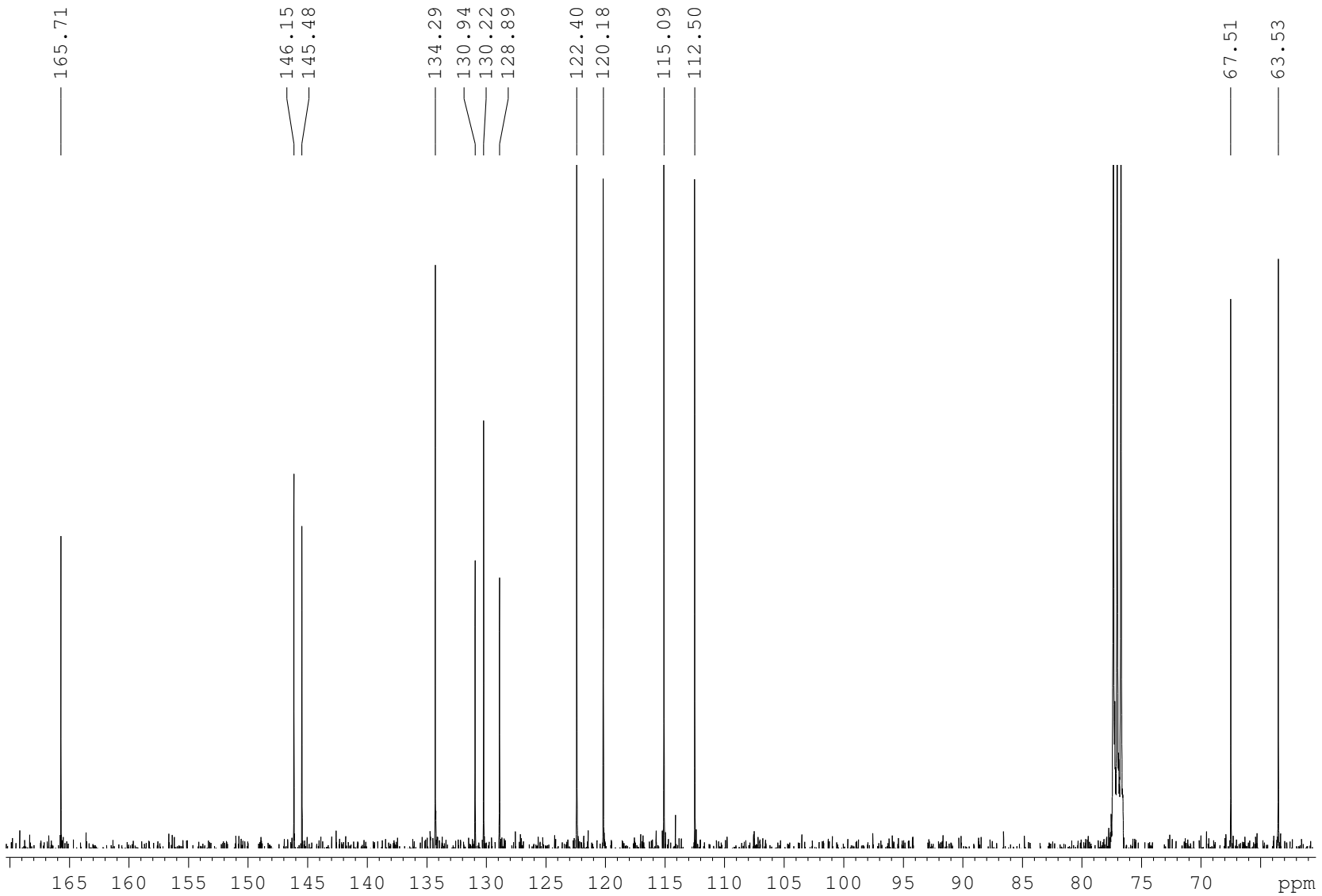

200
180
160
140
120
100
80
60
40
20
0
ppm
165.766
146.154
145.462
133.704
129.789
122.466
120.188
115.095
112.491
67.488
63.670
165
160
155
150
145
140
135
130
125
120
115
ppm
70
68
66
64
ppm

Compound: **355**

Bis(2-(2-Hydroxyphenoxy)ethyl)isophthalate

^{1}H and ^{13}C NMR

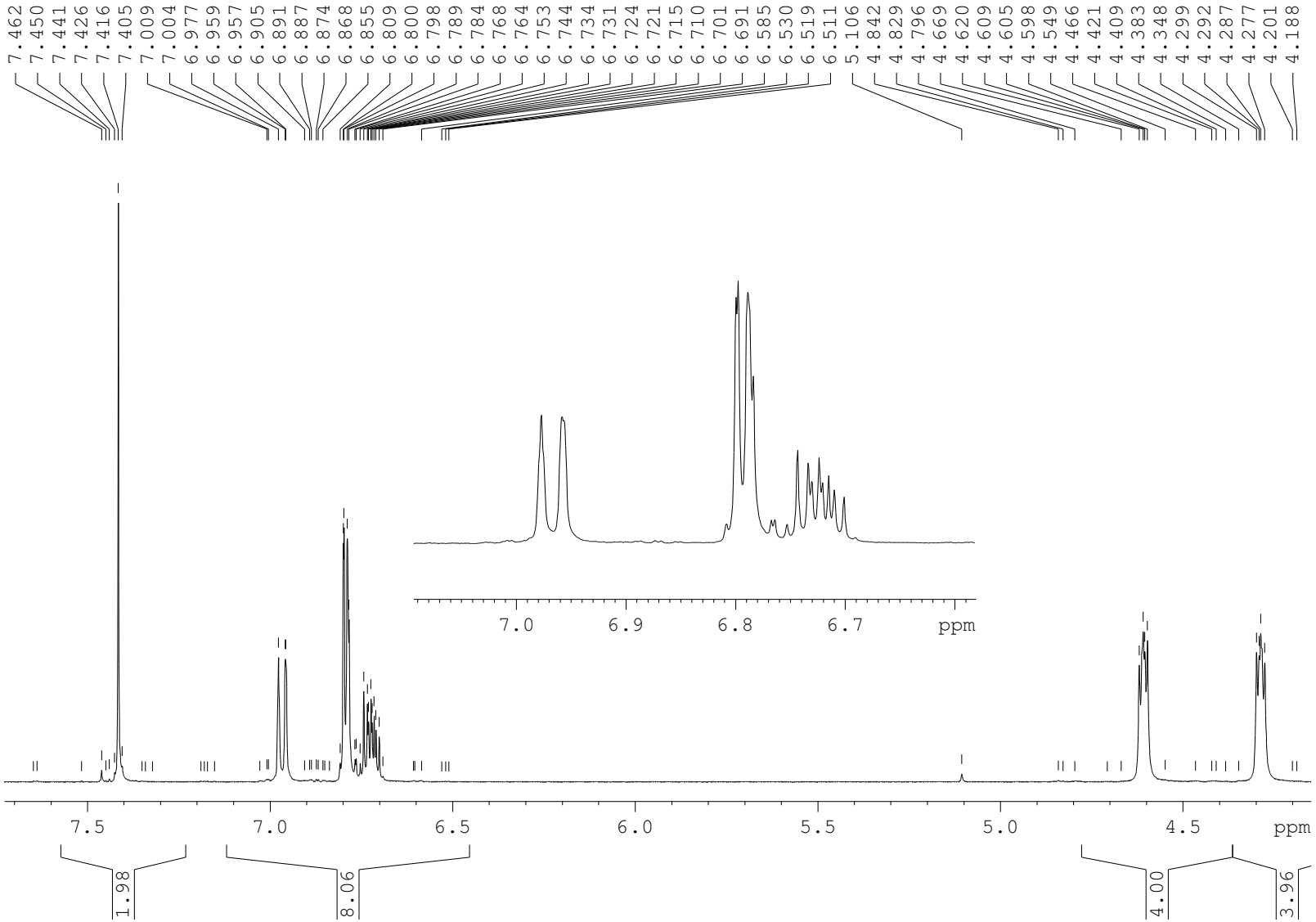

8.634
8.631
8.627
8.177
8.173
8.158
8.153
7.486
7.467
7.447
6.881
6.877
6.861
6.856
6.846
6.841
6.839
6.835
6.829
6.825
6.819
6.815
6.808
6.803
6.785
6.781
6.775
6.769
6.764
6.762
6.748
6.743
4.676
4.664
4.661
4.658
4.653
4.337
4.329
4.326
4.314
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm
0.94
2.01
1.00
5.97
2.05
4.00
4.01

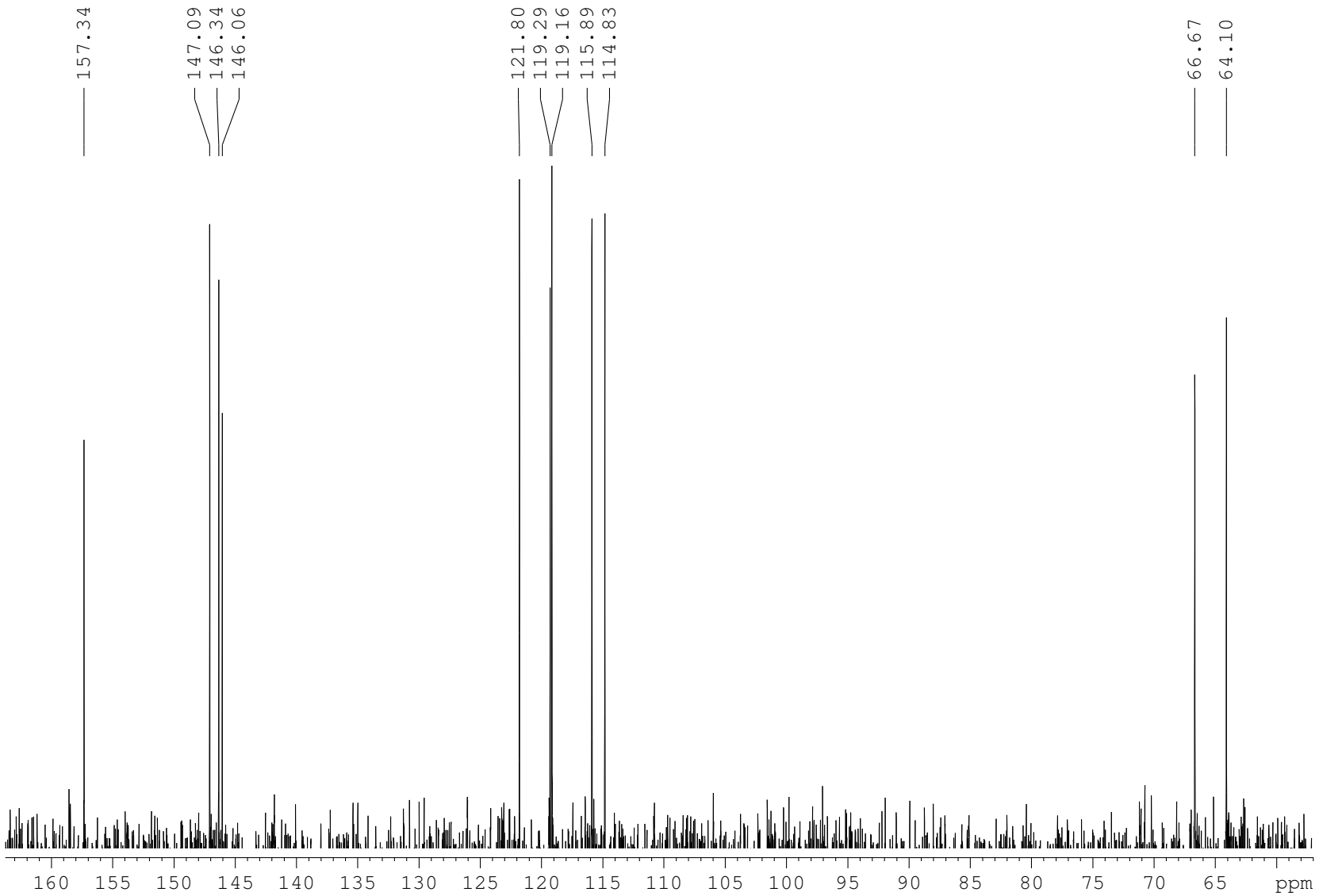

165.71
146.15
145.48
134.29
130.94
130.22
128.89
122.40
120.18
115.09
112.50
67.51
63.53
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70
ppm

Compound: **356**

Bis(2-(2-hydroxyphenoxy)ethyl)furan-2,5-dicarboxylate

^{1}H and ^{13}C NMR

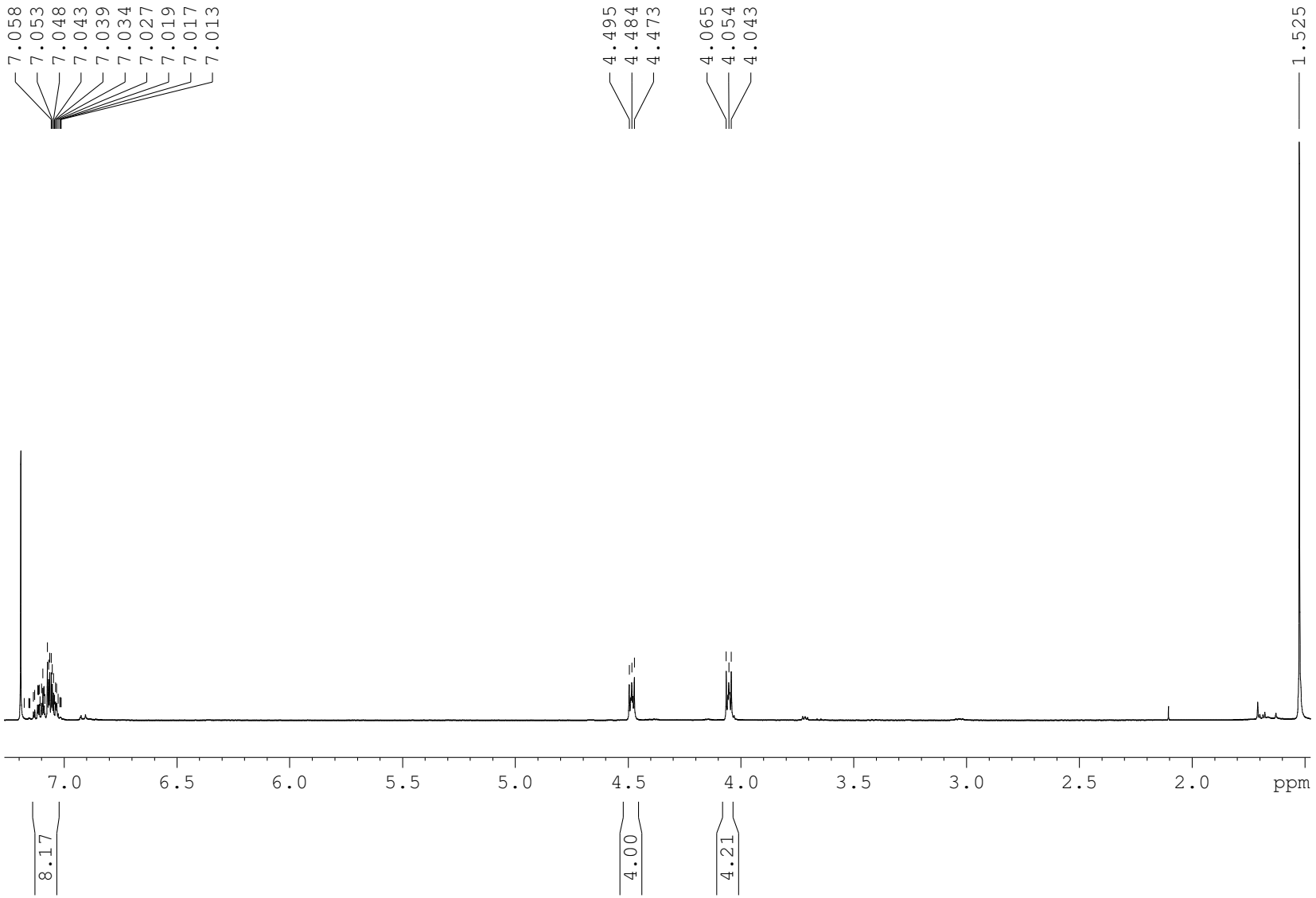

7.462
7.450
7.441
7.426
7.416
7.405
7.009
7.004
6.977
6.959
6.957
6.905
6.891
6.887
6.874
6.868
6.855
6.809
6.800
6.798
6.789
6.784
6.768
6.764
6.753
6.744
6.734
6.731
6.724
6.721
6.715
6.710
6.701
6.691
6.585
6.530
6.519
6.511
5.106
4.842
4.829
4.796
4.669
4.620
4.609
4.605
4.598
4.549
4.466
4.421
4.409
4.383
4.348
4.299
4.292
4.287
4.277
4.201
4.188
7.0
6.9
6.8
6.7
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm
1.98
8.06
4.00
3.96

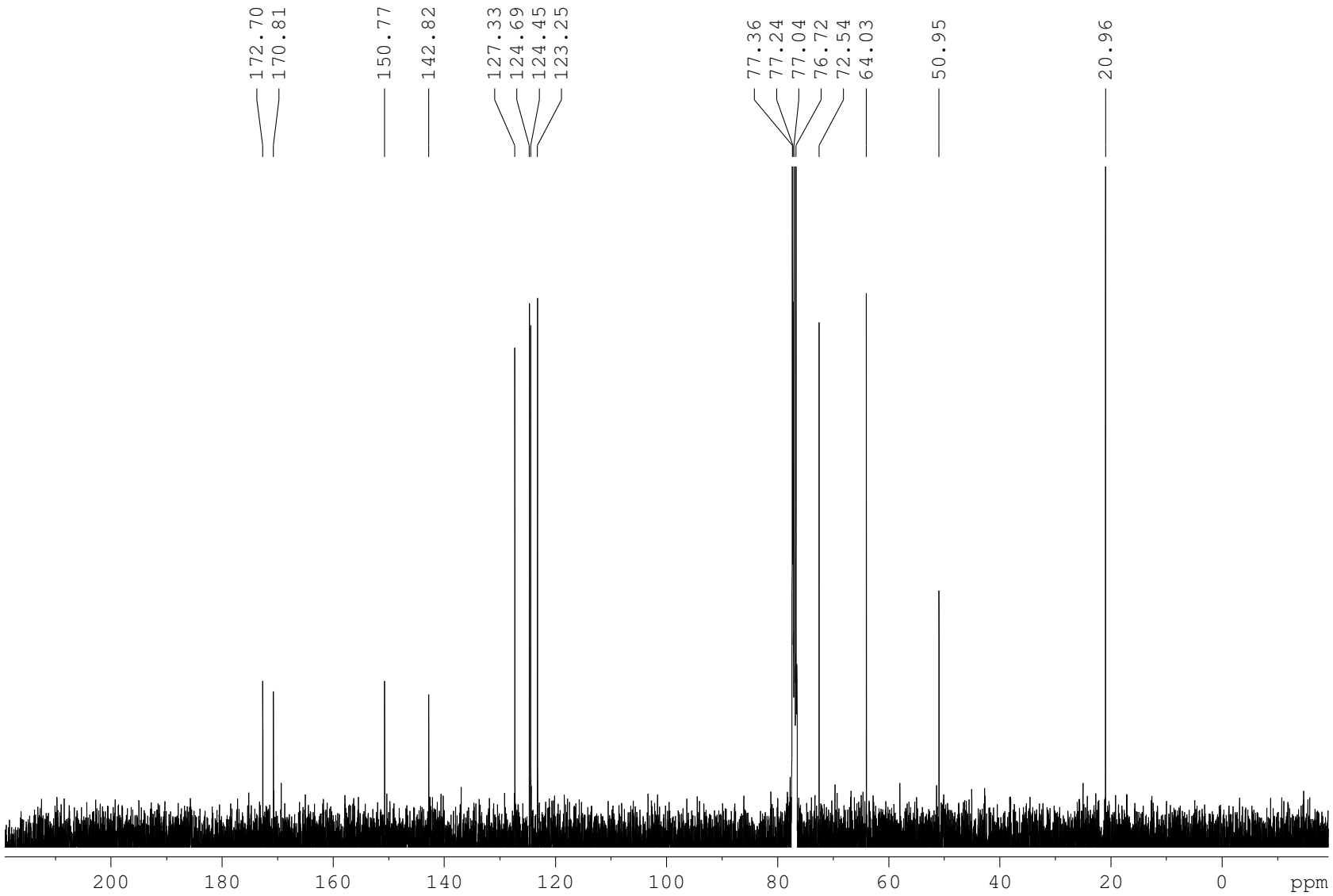

157.34
147.09
146.34
146.06
121.80
119.29
119.16
115.89
114.83
66.67
64.10
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 ppm

Compound: **357**

2,3,9,10-dibenzo-6,16-tetramethyl-1,4,8,11,14,18-hexaoxacyclohexaeicosa-2,9-diene-5,7,15,17-tetraone

^{1}H and ^{13}C NMR

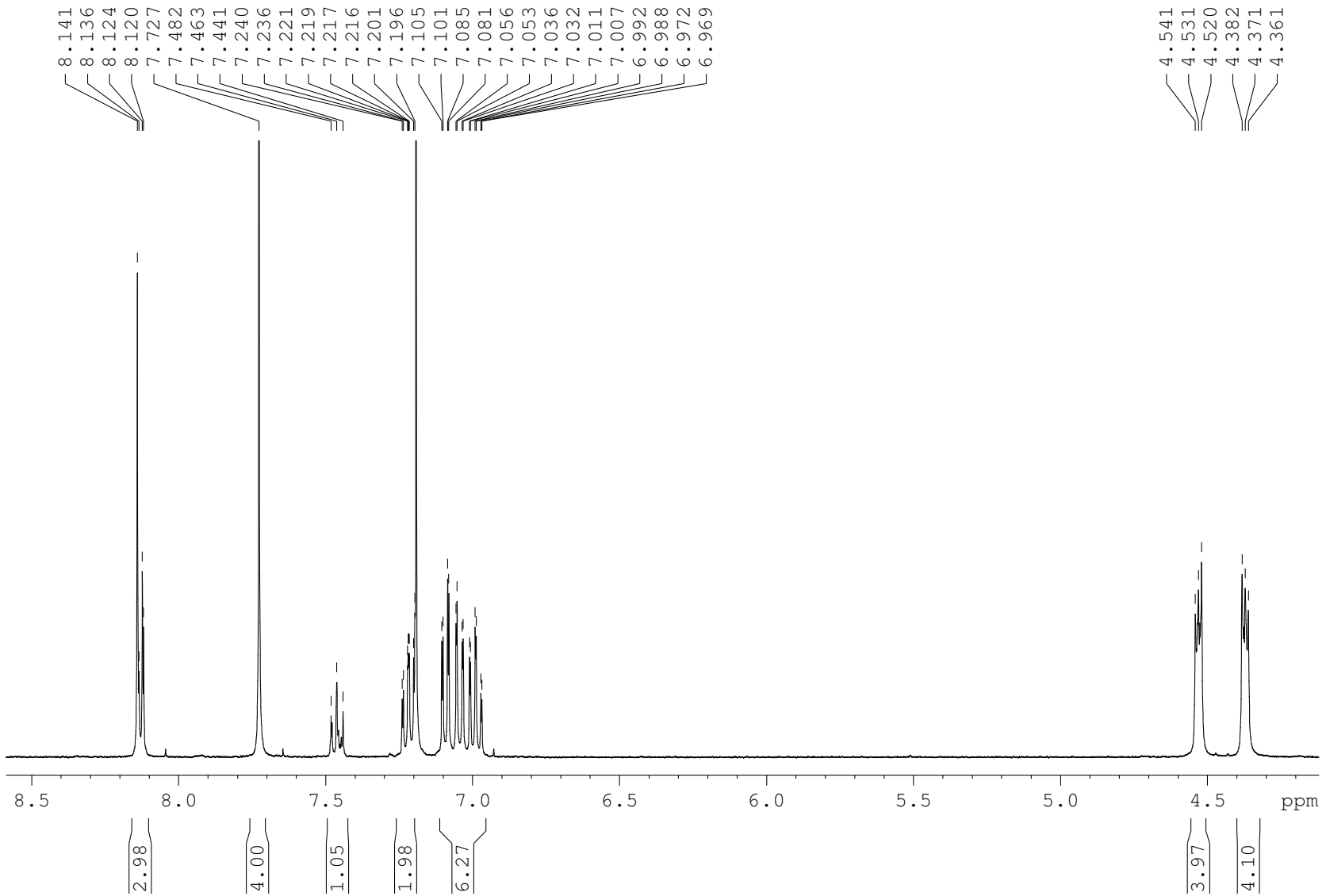

7.058
7.053
7.048
7.043
7.039
7.034
7.027
7.019
7.017
7.013
4.495
4.484
4.473
4.065
4.054
4.043
1.525
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
8.17
4.00
4.21

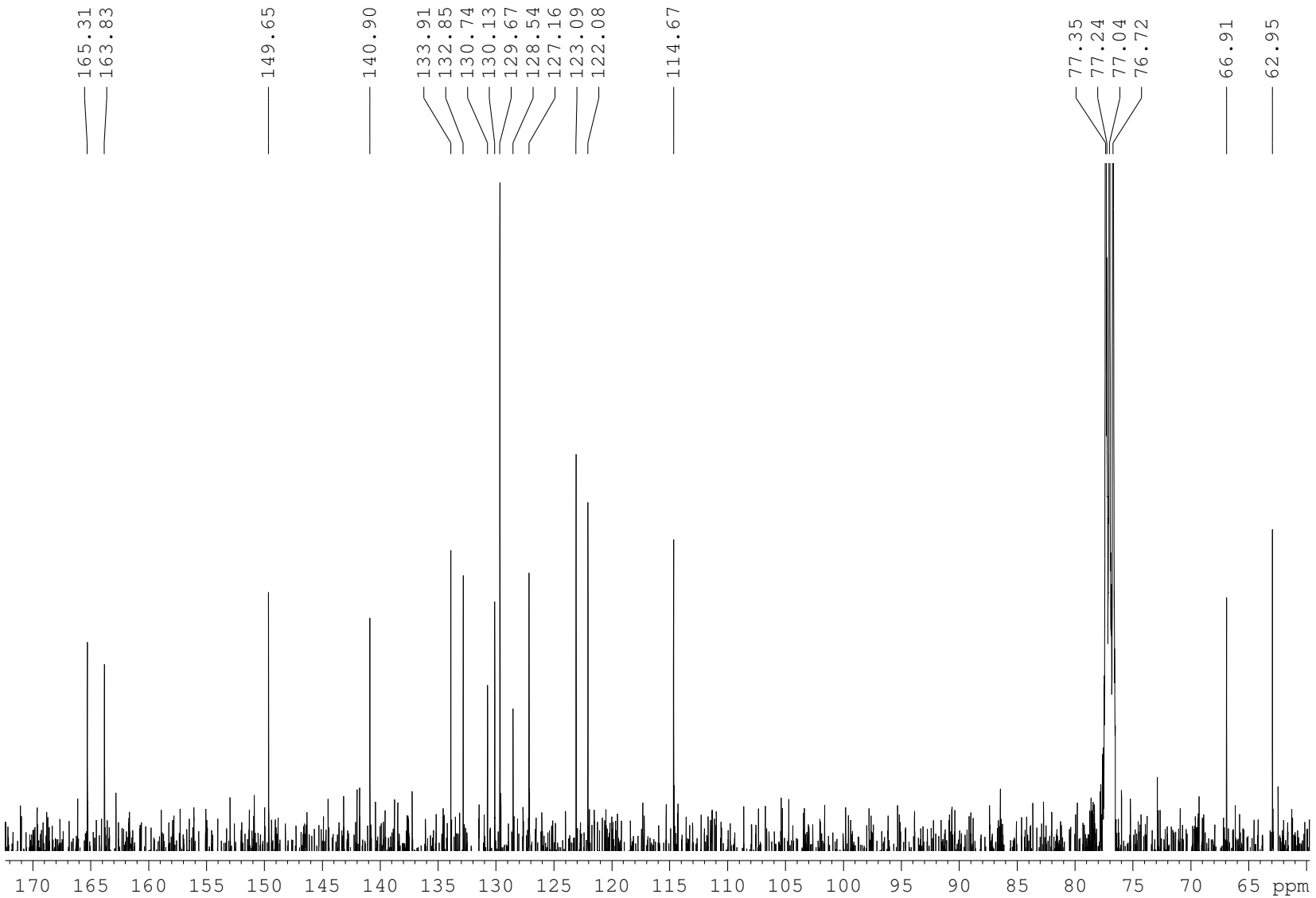

172.70
170.81
150.77
142.82
127.33
124.69
124.45
123.25
77.36
77.24
77.04
76.72
72.54
64.03
50.95
20.96
200
180
160
140
120
100
80
60
40
20
0
ppm

Compound: **358**

2,3,6,9,11,12,13,19,21-tetrabenzo-1,4,11,14,17,23-hexaoxacyclopentaeicosa-2,6,8,12,19-pentaene-5,10,18,22-tetraone

^{1}H and ^{13}C NMR

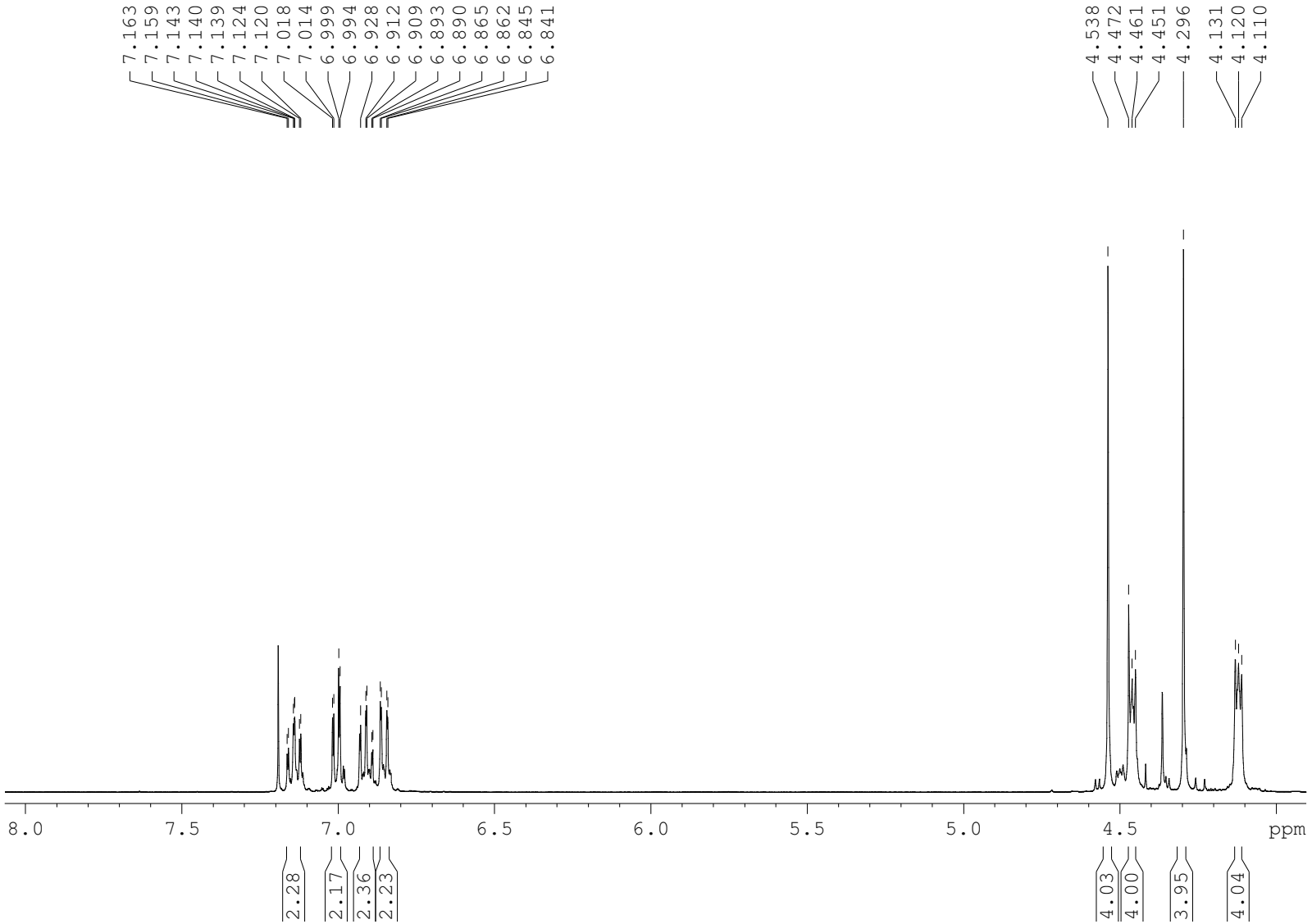

8.141
8.136
8.124
8.120
7.727
7.482
7.463
7.441
7.240
7.236
7.221
7.219
7.217
7.216
7.201
7.196
7.105
7.101
7.085
7.081
7.056
7.053
7.036
7.032
7.011
7.007
6.992
6.988
6.972
6.969
4.541
4.531
4.520
4.382
4.371
4.361
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm
2.98
4.00
1.05
1.98
6.27
3.97
4.10

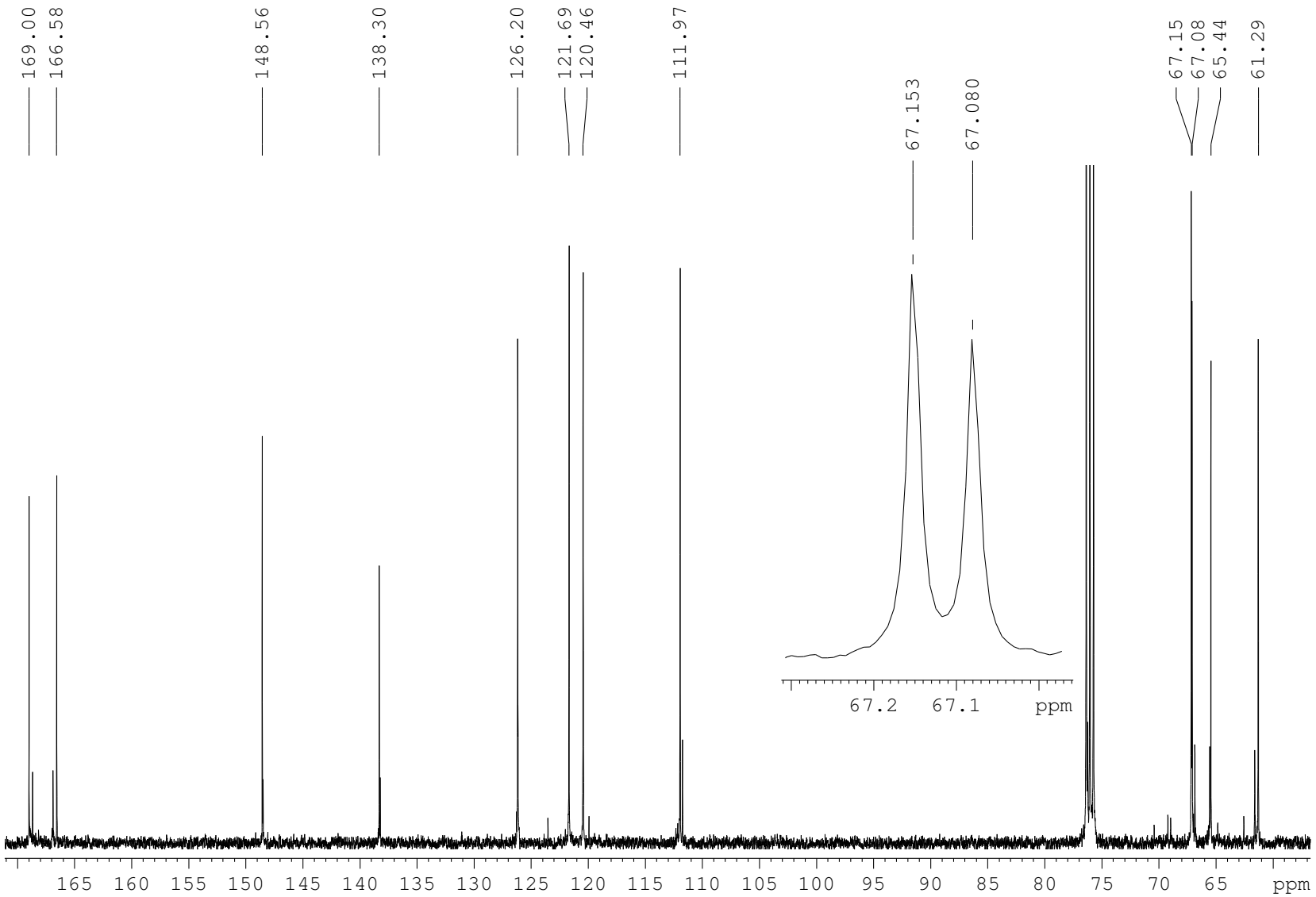

165.31
163.83
149.65
140.90
133.91
132.85
130.74
130.13
129.67
128.54
127.16
123.09
122.08
114.67
77.35
77.24
77.04
76.72
66.91
62.95
170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 ppm

Compound: **359**

2,3,11,12-dibenzo-1,4,7,10,13,16,19,22-octaoxacyclotetraeicosa-2,11-diene-5,9,17,21-tetraone

^{1}H and ^{13}C NMR


7.163
7.159
7.143
7.140
7.139
7.124
7.120
7.018
7.014
6.999
6.994
6.928
6.912
6.909
6.893
6.890
6.865
6.862
6.845
6.841
4.538
4.472
4.461
4.451
4.296
4.131
4.120
4.110
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm
2.28
2.17
2.36
2.23
4.03
4.00
3.95
4.04

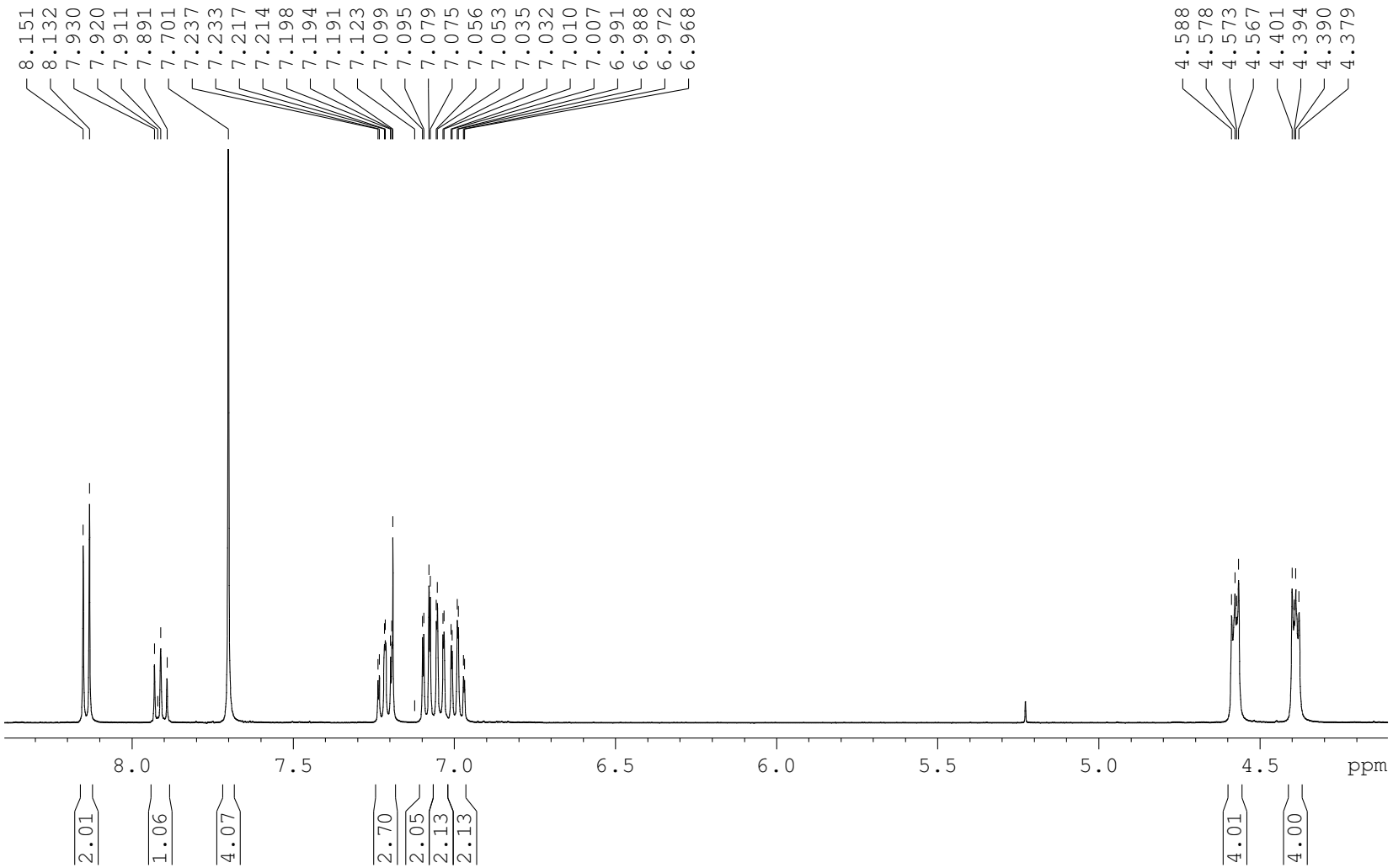

169.00
166.58
148.56
138.30
126.20
121.69
120.46
111.97
67.153
67.080
67.15
67.08
65.44
61.29
67.2
67.1
ppm
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65
ppm

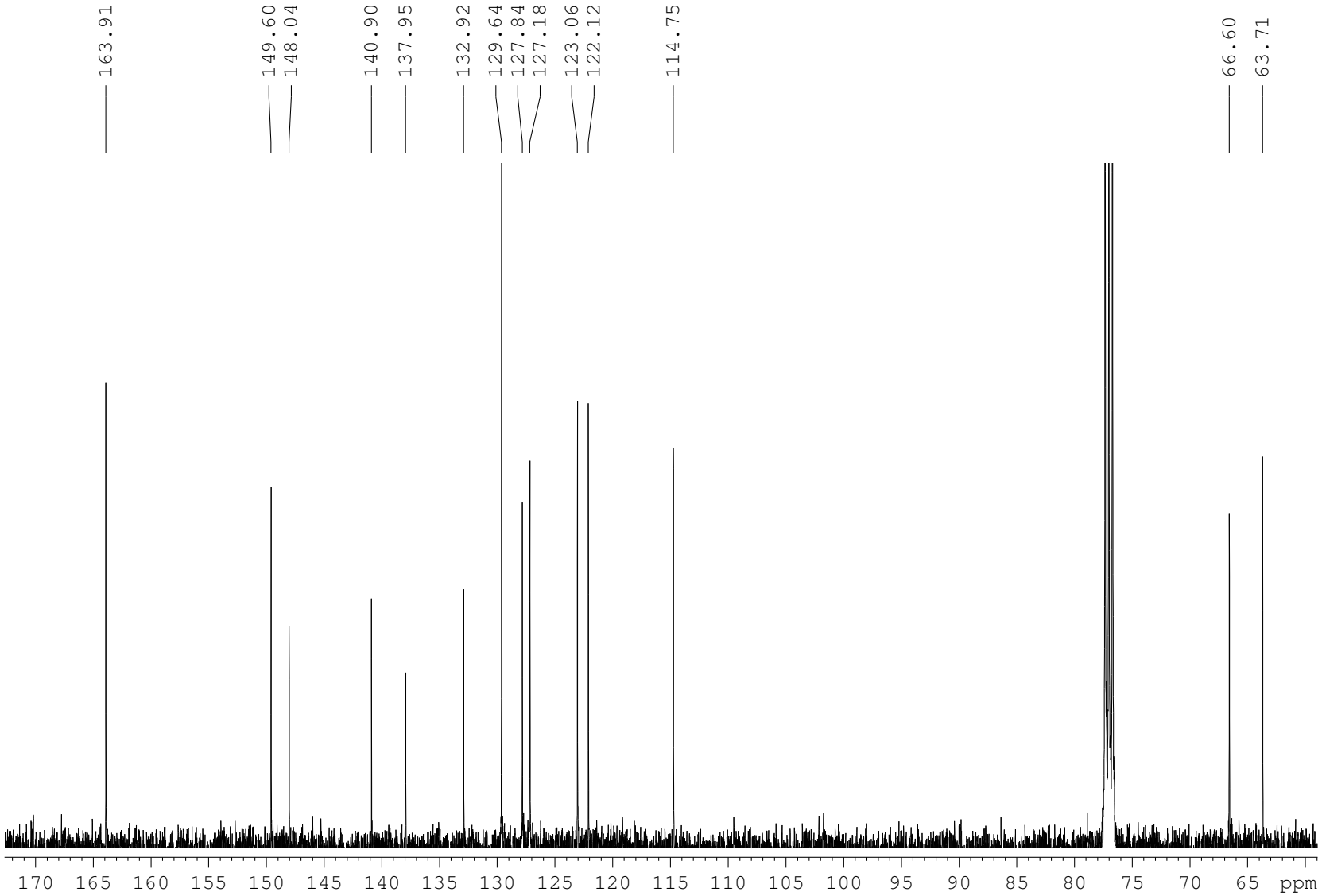
Compound: **360**

2,3,6,9,12,13,19,21-tetrabenzo-20-aza-1,4,11,14,17,23-hexaoxacyclopentaeicosa-2,6,8,12,19-pentaene-5,10,18,22-tetraone

^{1}H and ^{13}C NMR

Para Pyri

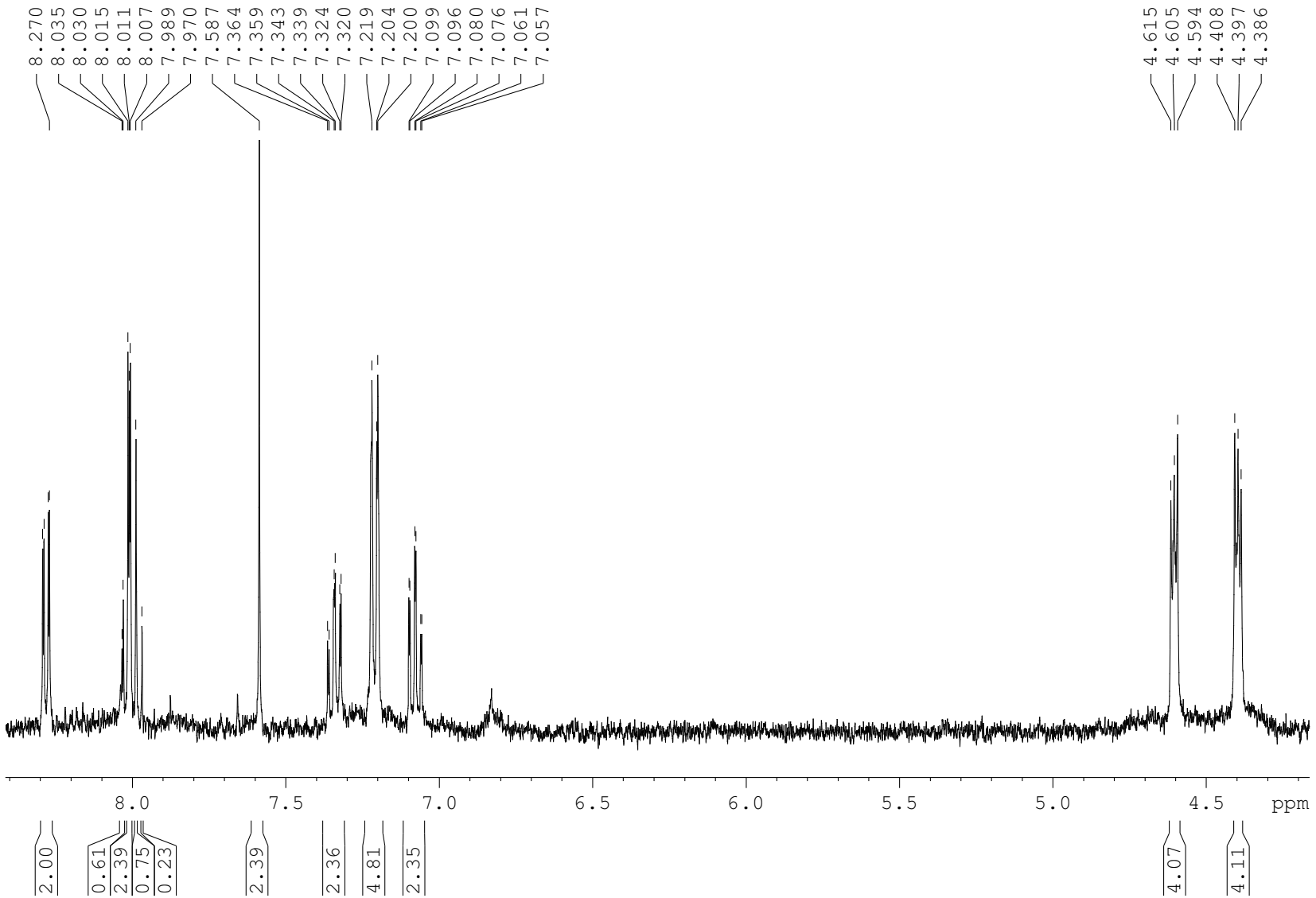

8.151
8.132
7.930
7.920
7.911
7.891
7.701
7.237
7.233
7.217
7.214
7.198
7.194
7.191
7.123
7.099
7.095
7.079
7.075
7.056
7.053
7.035
7.032
7.010
7.007
6.991
6.988
6.972
6.968
4.588
4.578
4.573
4.567
4.401
4.394
4.390
4.379
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm
2.01
1.06
4.07
2.70
2.05
2.13
2.13
4.01
4.00


163.91
149.60
148.04
140.90
137.95
132.92
129.64
127.84
127.18
123.06
122.12
114.75
66.60
63.71
170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 ppm

Compound: **361**

2,3,6,8,11,12,18,21-tetrabenzo-7-aza-1,4,10,13,16,23-hexaoxacyclopentaeicosa-2,6,11,18,20-pentaene-5,9,17,21-tetraone

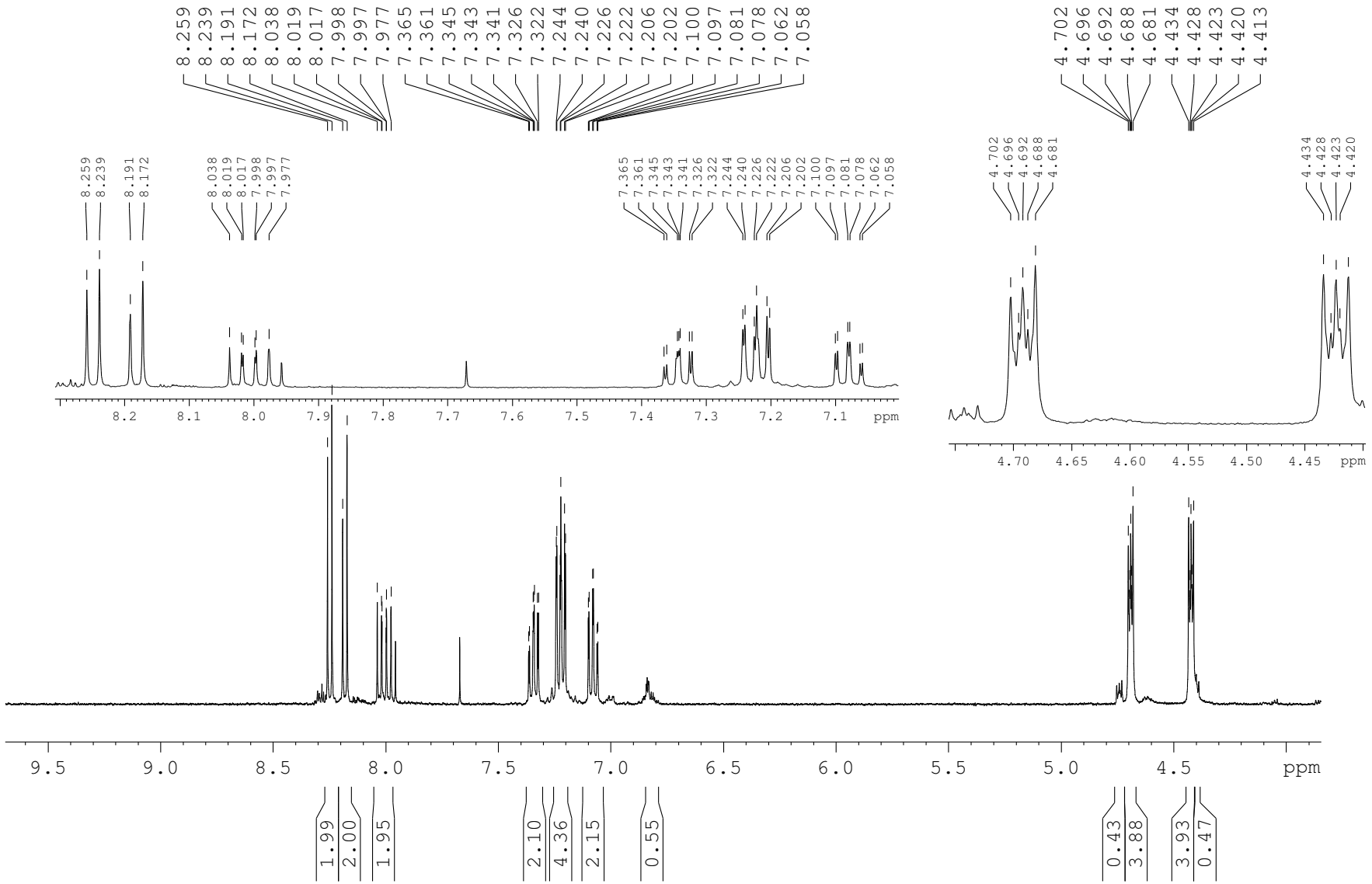
^{1}H and ^{13}C NMR

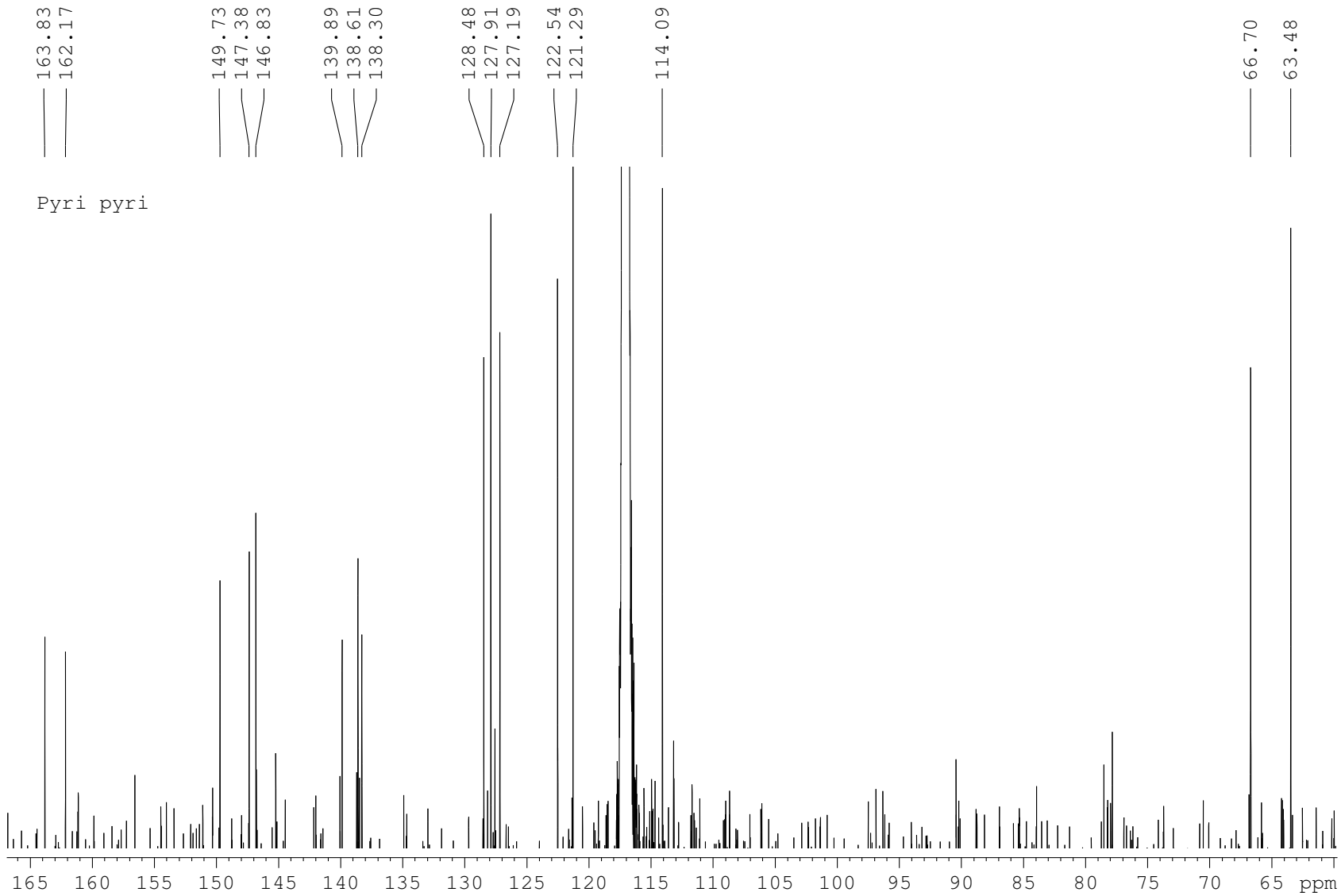

8.270
8.035
8.030
8.015
8.011
8.007
7.989
7.970
7.587
7.364
7.359
7.343
7.339
7.324
7.320
7.219
7.204
7.200
7.099
7.096
7.080
7.076
7.061
7.057
4.615
4.605
4.594
4.408
4.397
4.386
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
ppm
2.00
0.61
2.39
0.75
0.23
2.39
2.36
4.81
2.35
4.07
4.11

Compound: **362**

2,3,6,8,11,12,18,20-tetrabenzo-7,19-diaza-1,4,10,13,16,22-hexaoxacyclotetraeicosa-2,6,11,18-tetraene-5,9,17,21-tetraone

^{1}H and ^{13}C NMR

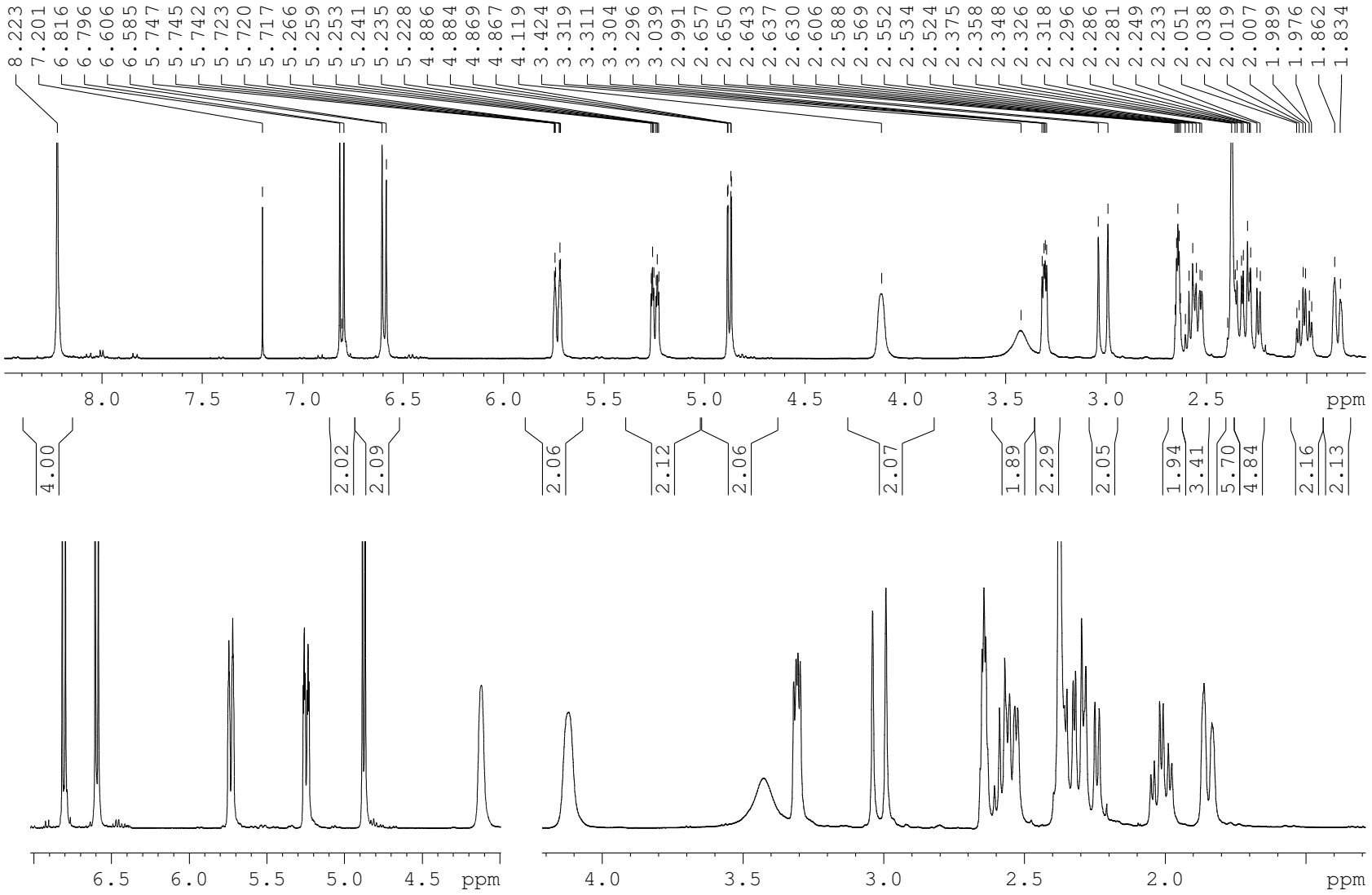

8.259
8.239
8.191
8.172
8.038
8.019
8.017
7.998
7.997
7.977
7.365
7.361
7.345
7.343
7.341
7.326
7.322
7.244
7.240
7.226
7.222
7.206
7.202
7.100
7.097
7.081
7.078
7.062
7.058
4.702
4.696
4.692
4.688
4.681
4.434
4.428
4.423
4.420
4.413
ppm
1.99
2.00
1.95
2.10
4.36
2.15
0.55
0.43
3.88
3.93
0.47

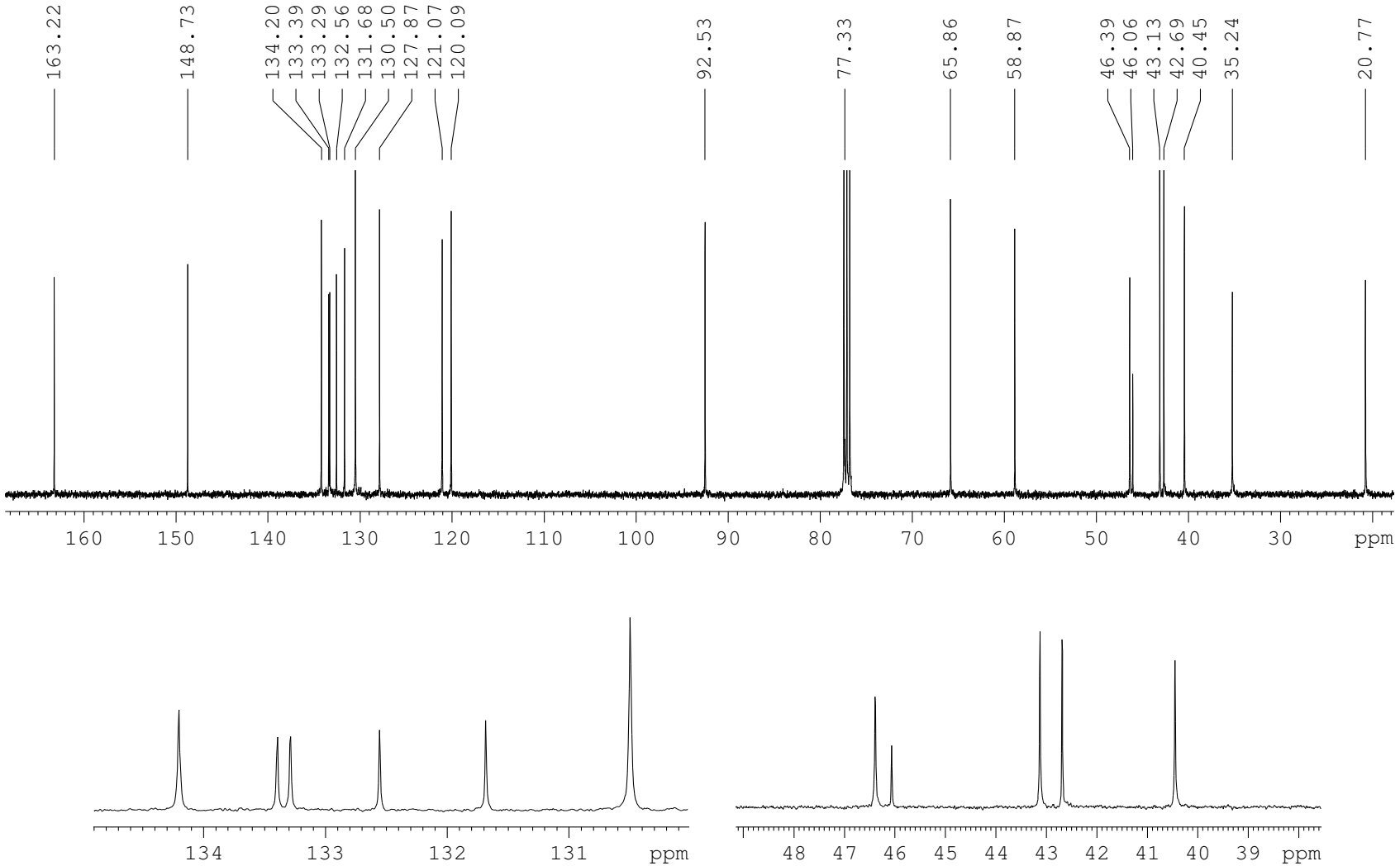

163.83
162.17
149.73
147.38
146.83
139.89
138.61
138.30
128.48
127.91
127.19
122.54
121.29
114.09
66.70
63.48
Pyri pyri
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 ppm

Compound: **368**

bis(3-morphinyl) terephthalate

^{1}H and ^{13}C NMR

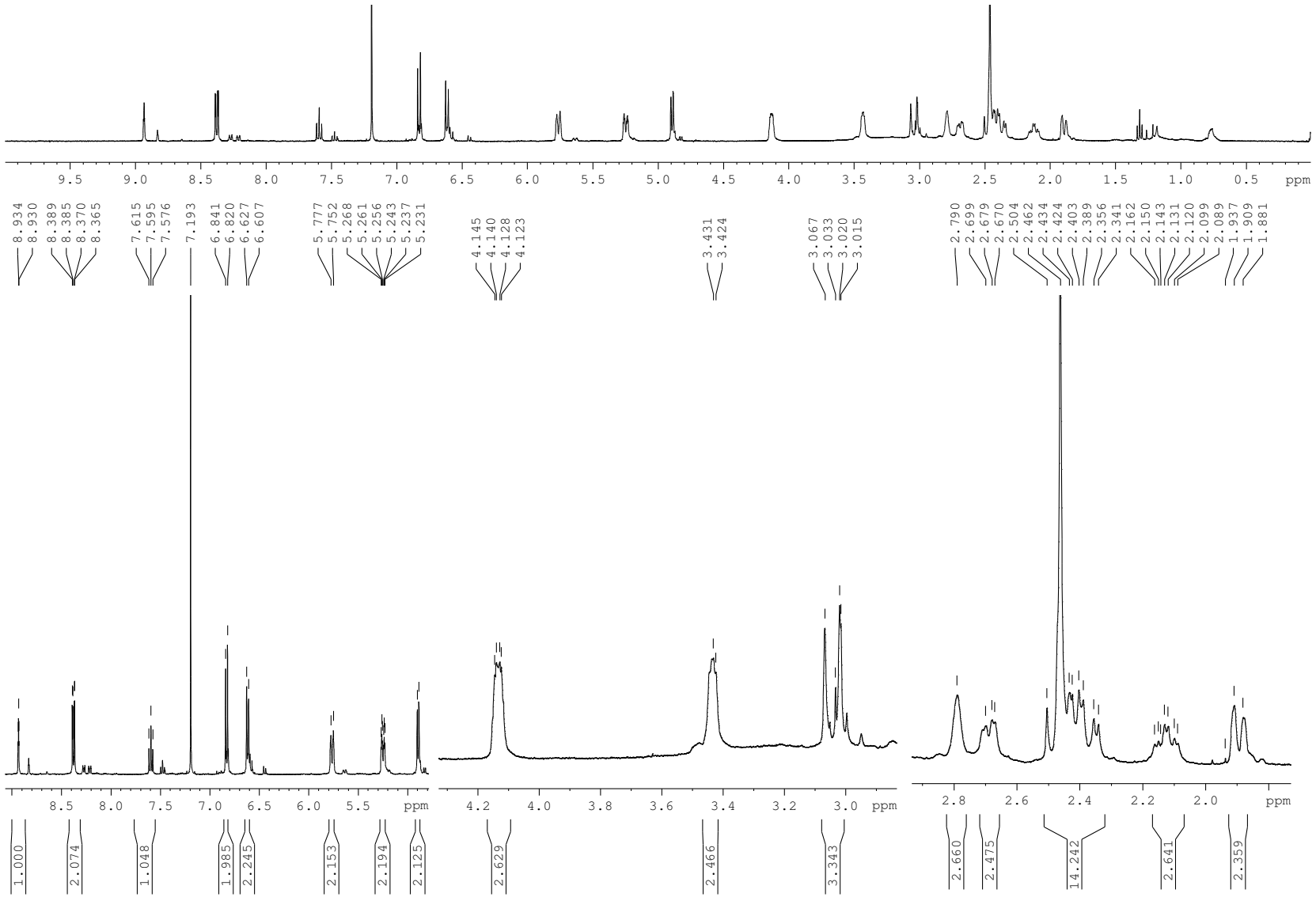

8.223
7.201
6.816
6.796
6.606
6.585
5.747
5.745
5.742
5.723
5.720
5.717
5.266
5.259
5.253
5.241
5.235
5.228
4.886
4.884
4.869
4.867
4.119
3.424
3.319
3.311
3.304
3.296
3.039
2.991
2.657
2.650
2.643
2.637
2.630
2.606
2.588
2.569
2.552
2.534
2.524
2.375
2.358
2.348
2.326
2.318
2.296
2.286
2.281
2.249
2.233
2.051
2.038
2.019
2.007
1.989
1.976
1.862
1.834
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
4.00
2.02
2.09
2.06
2.12
2.06
2.07
1.89
2.29
2.05
1.94
3.41
5.70
4.84
2.16
2.13
6.5
6.0
5.5
5.0
4.5
ppm
4.0
3.5
3.0
2.5
2.0
ppm

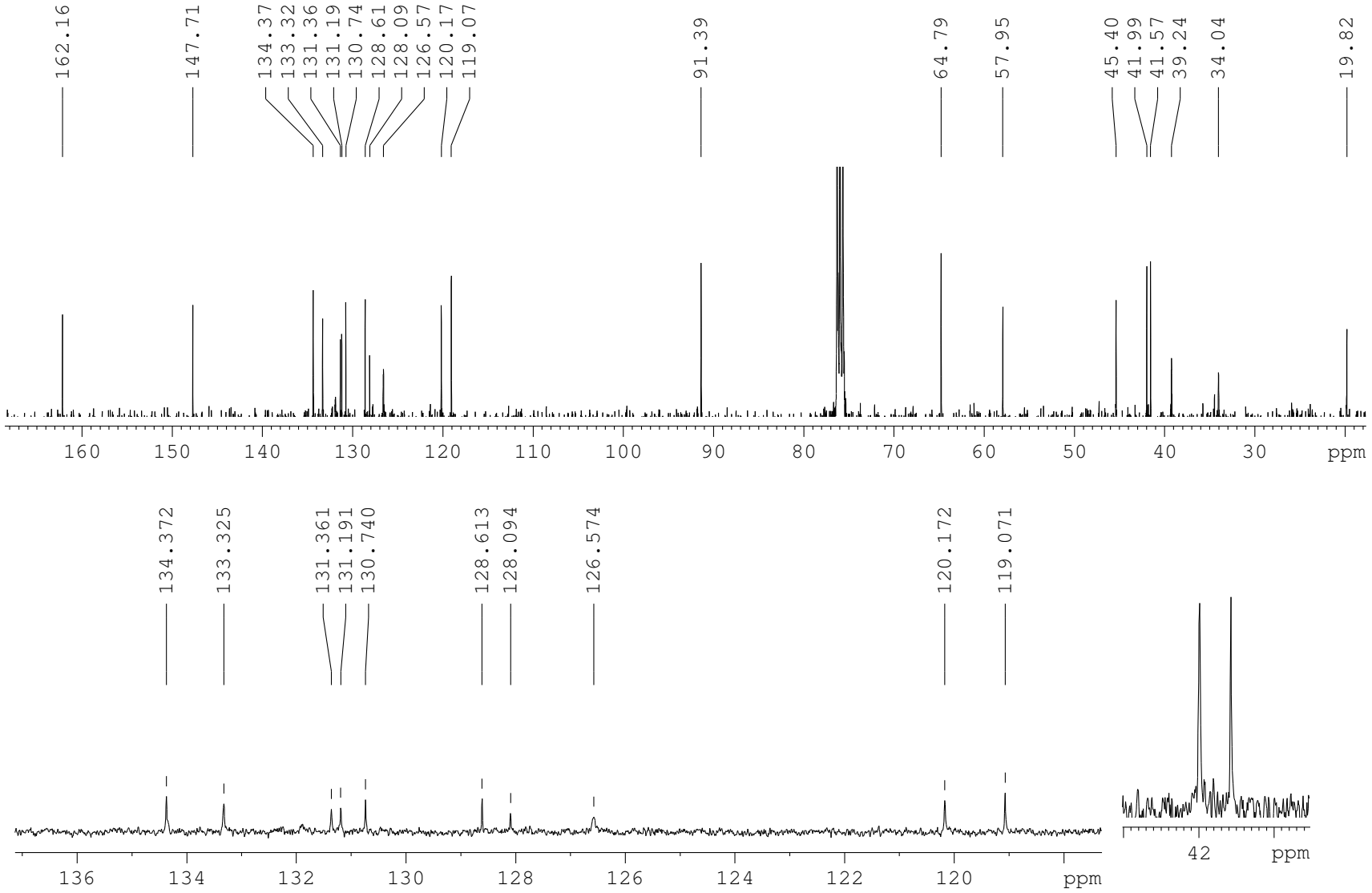

163.22
148.73
134.20
133.39
133.29
132.56
131.68
130.50
127.87
121.07
120.09
92.53
77.33
65.86
58.87
46.39
46.06
43.13
42.69
40.45
35.24
20.77
160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm
134 133 132 131 ppm
48 47 46 45 44 43 42 41 40 39 ppm

Compound: **369**

bis(3-morphinyl) isophthalate

^{1}H and ^{13}C NMR

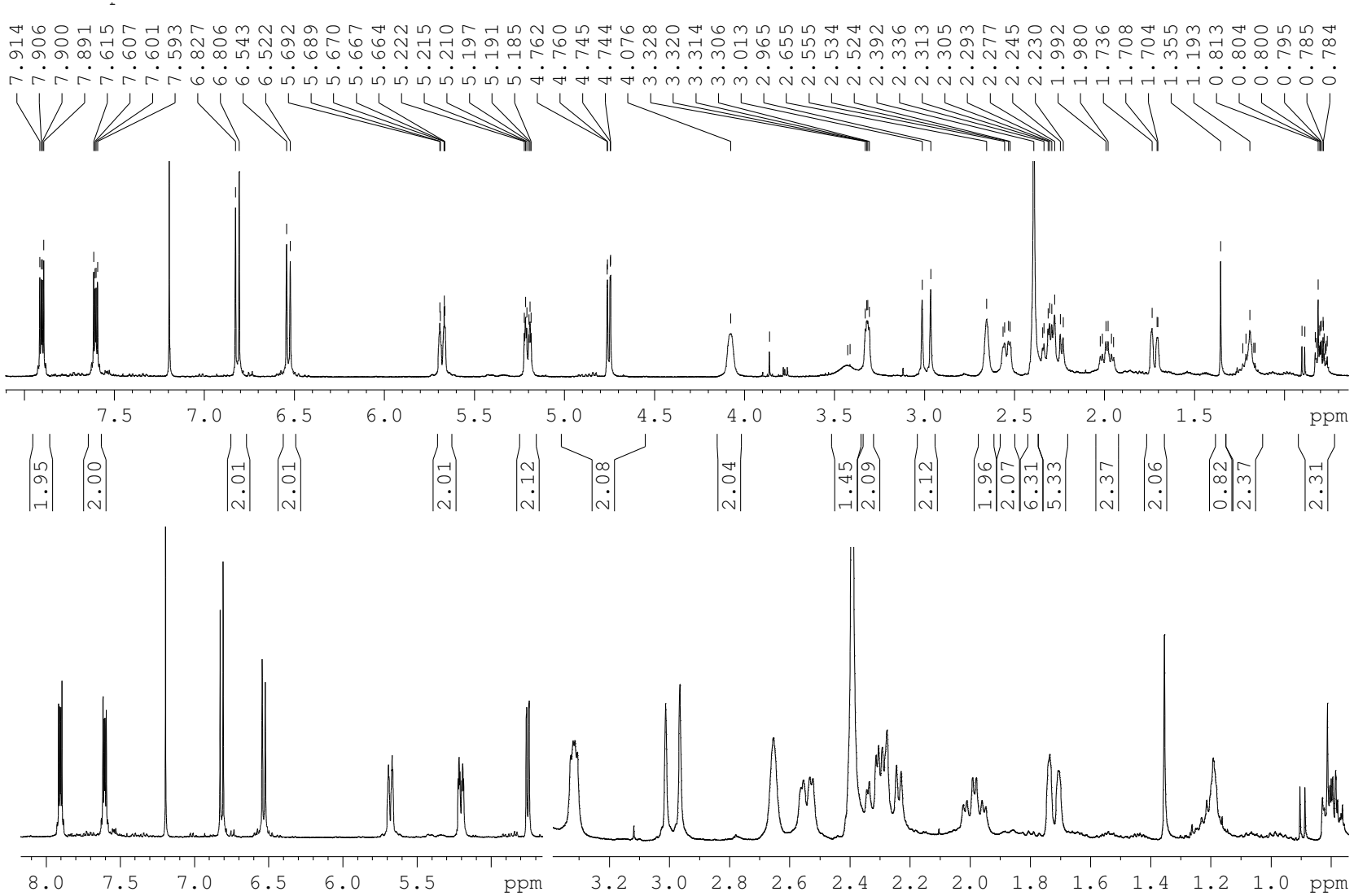

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
8.934 8.930 8.389 8.385 8.370 8.365 7.615 7.595 7.576 7.193 6.841 6.820 6.627 6.607 5.777 5.752 5.268 5.261 5.256 5.243 5.237 5.231 4.145 4.140 4.128 4.123 3.431 3.424 3.067 3.033 3.020 3.015 2.790 2.699 2.679 2.670 2.504 2.462 2.434 2.424 2.403 2.389 2.356 2.341 2.162 2.150 2.143 2.131 2.120 2.099 2.089 1.937 1.909 1.881
8.5 8.0 7.5 7.0 6.5 6.0 5.5 ppm
4.2 4.0 3.8 3.6 3.4 3.2 3.0 ppm
2.8 2.6 2.4 2.2 2.0 ppm
1.000 2.074 1.048 1.985 2.245 2.153 2.194 2.125 2.629 2.466 3.343 2.660 2.475 14.242 2.641 2.359

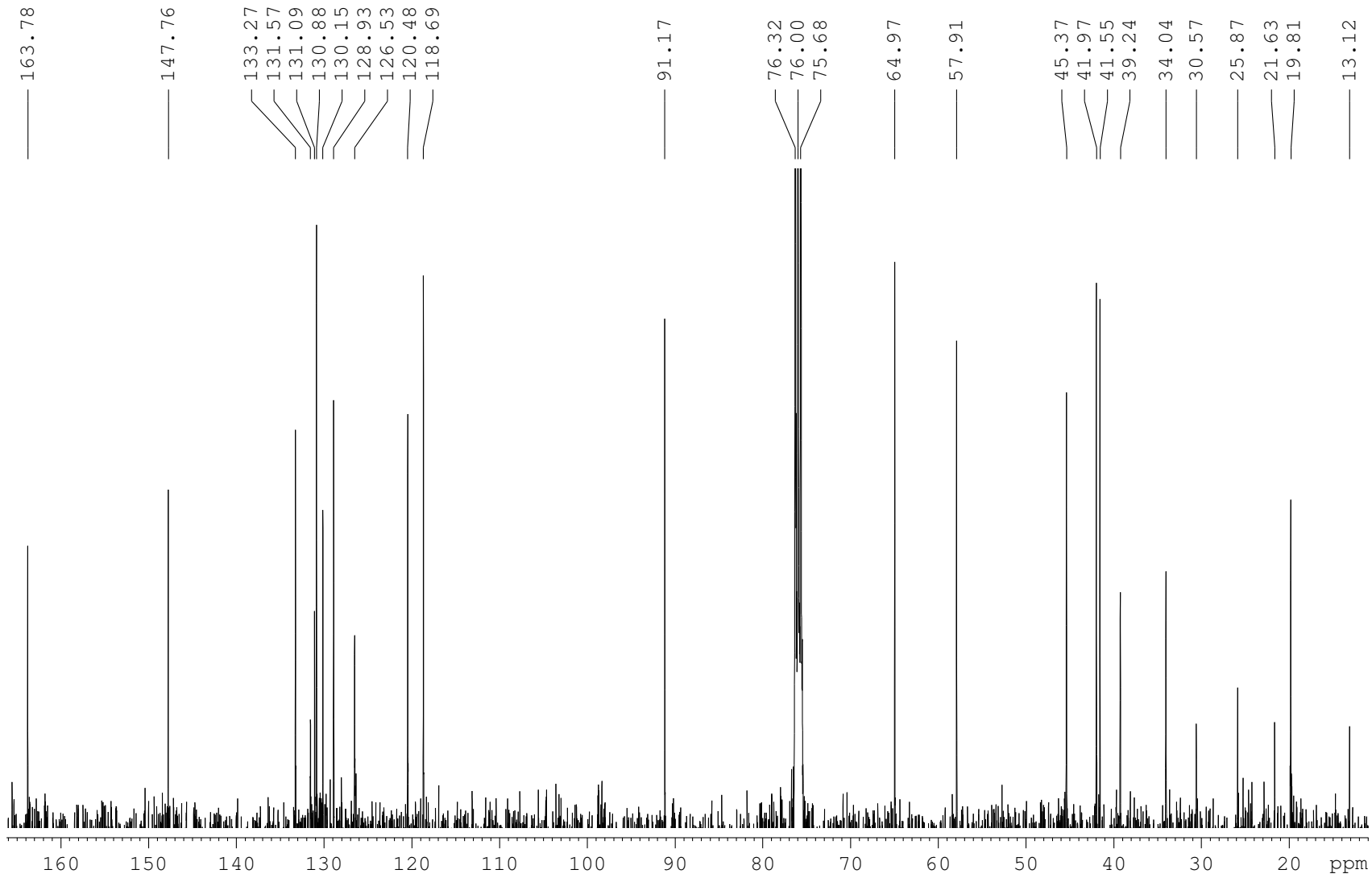

162.16
147.71
134.37
133.32
131.36
131.19
130.74
128.61
128.09
126.57
120.17
119.07
91.39
64.79
57.95
45.40
41.99
41.57
39.24
34.04
19.82
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm
134.372
133.325
131.361
131.191
130.740
128.613
128.094
126.574
120.172
119.071
136
134
132
130
128
126
124
122
120
ppm
42
ppm

Compound: **370**

bis(3-morphinyl) phthalate

^{1}H and ^{13}C NMR


7.914
7.906
7.900
7.891
7.615
7.607
7.601
7.593
6.827
6.806
6.543
6.522
5.692
5.689
5.670
5.667
5.664
5.222
5.215
5.210
5.197
5.191
5.185
4.762
4.760
4.745
4.744
4.076
3.328
3.320
3.314
3.306
3.013
2.965
2.655
2.555
2.534
2.524
2.392
2.336
2.313
2.305
2.293
2.277
2.245
2.230
1.992
1.980
1.736
1.708
1.704
1.355
1.193
0.813
0.804
0.800
0.795
0.785
0.784
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
1.95
2.00
2.01
2.01
2.01
2.12
2.08
2.04
1.45
2.09
2.12
1.96
2.07
6.31
5.33
2.37
2.06
0.82
2.37
2.31
8.0 7.5 7.0 6.5 6.0 5.5 ppm
3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 ppm

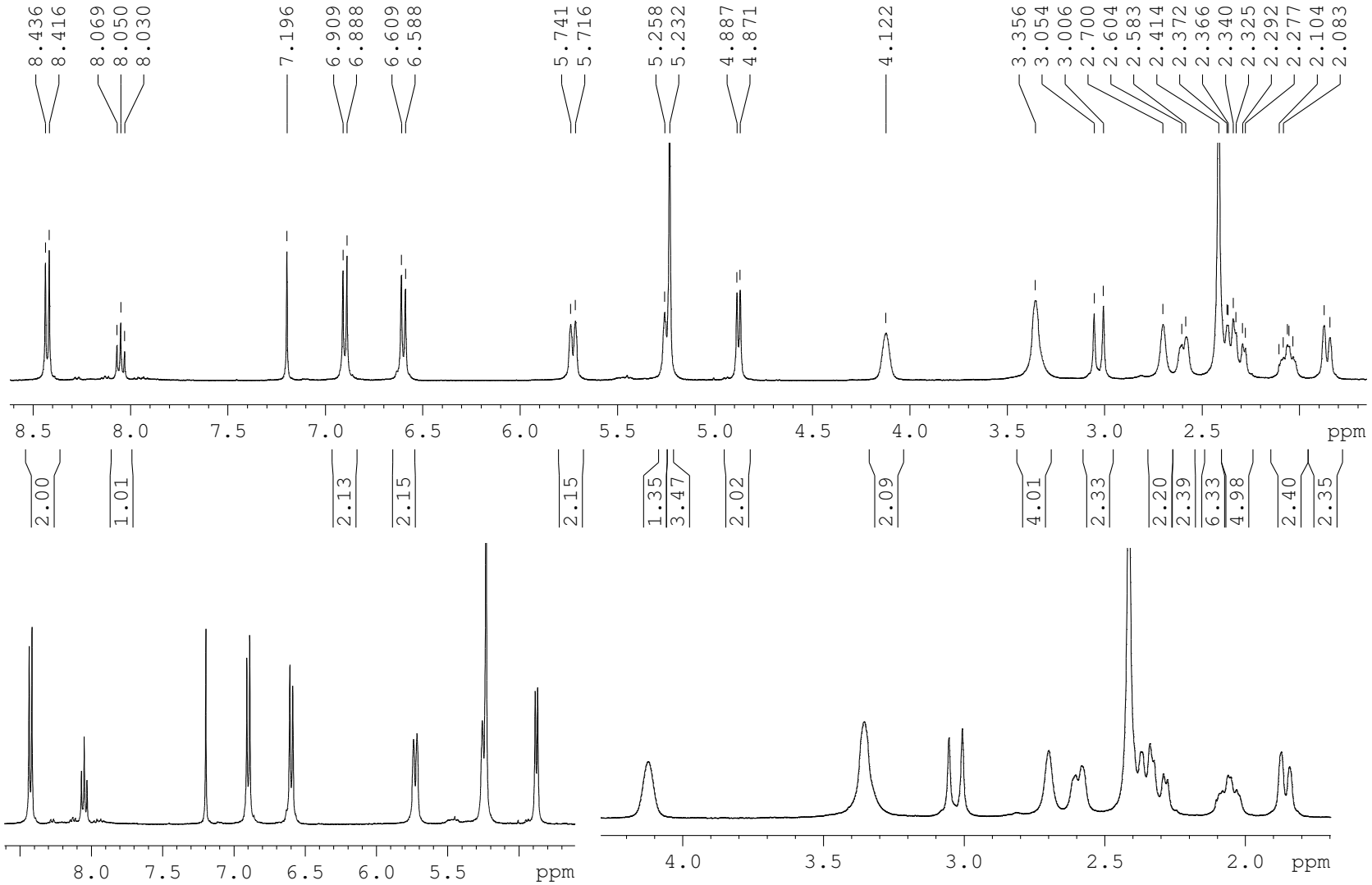

163.78
147.76
133.27
131.57
131.09
130.88
130.15
128.93
126.53
120.48
118.69
91.17
76.32
76.00
75.68
64.97
57.91
45.37
41.97
41.55
39.24
34.04
30.57
25.87
21.63
19.81
13.12
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

Compound: **371**

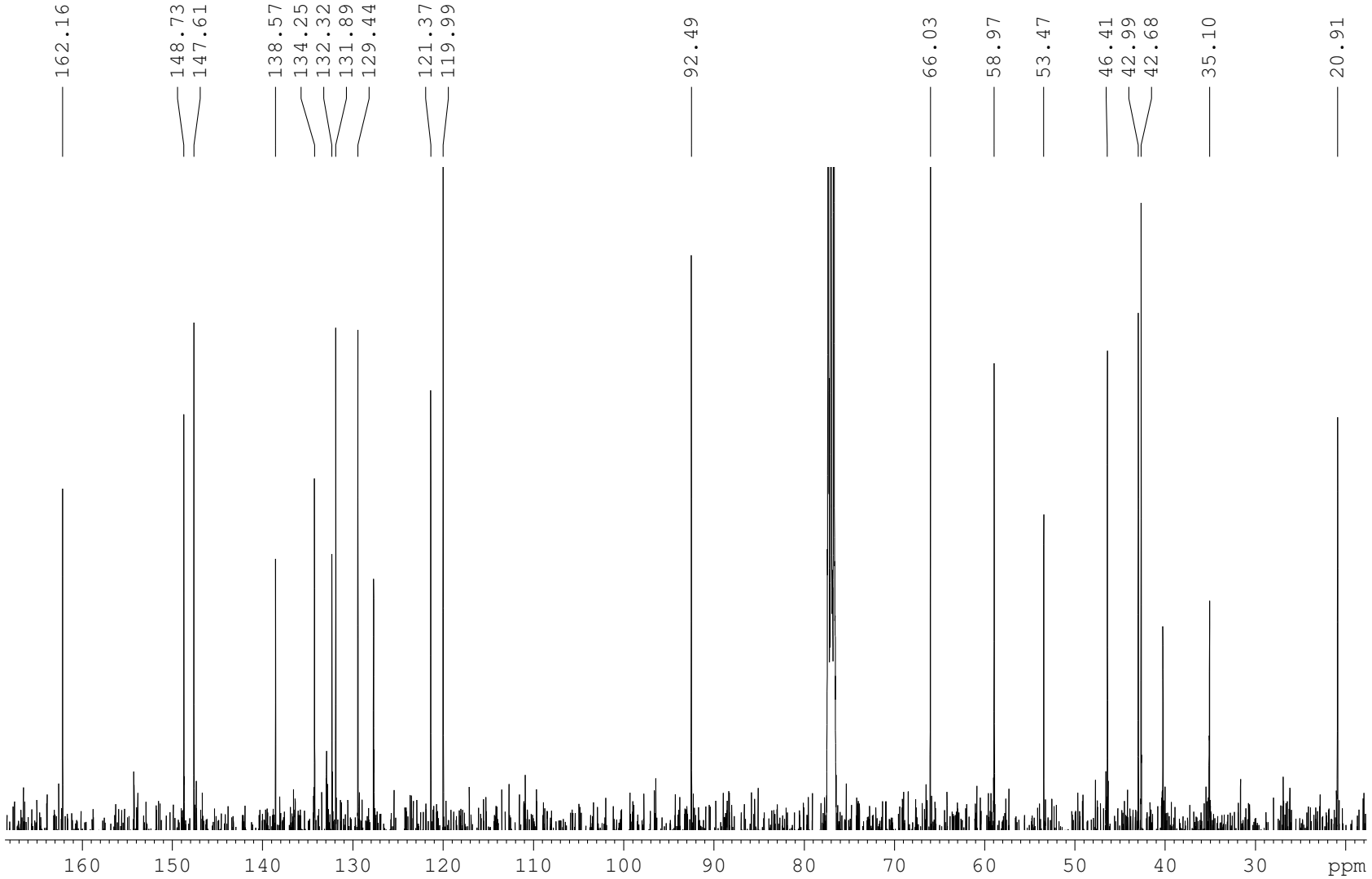
bis(3-morphinyl) pyridine-2,6-dicarboxylate

^{1}H and ^{13}C NMR

Pyridine Opiate



Pyridine Opiate

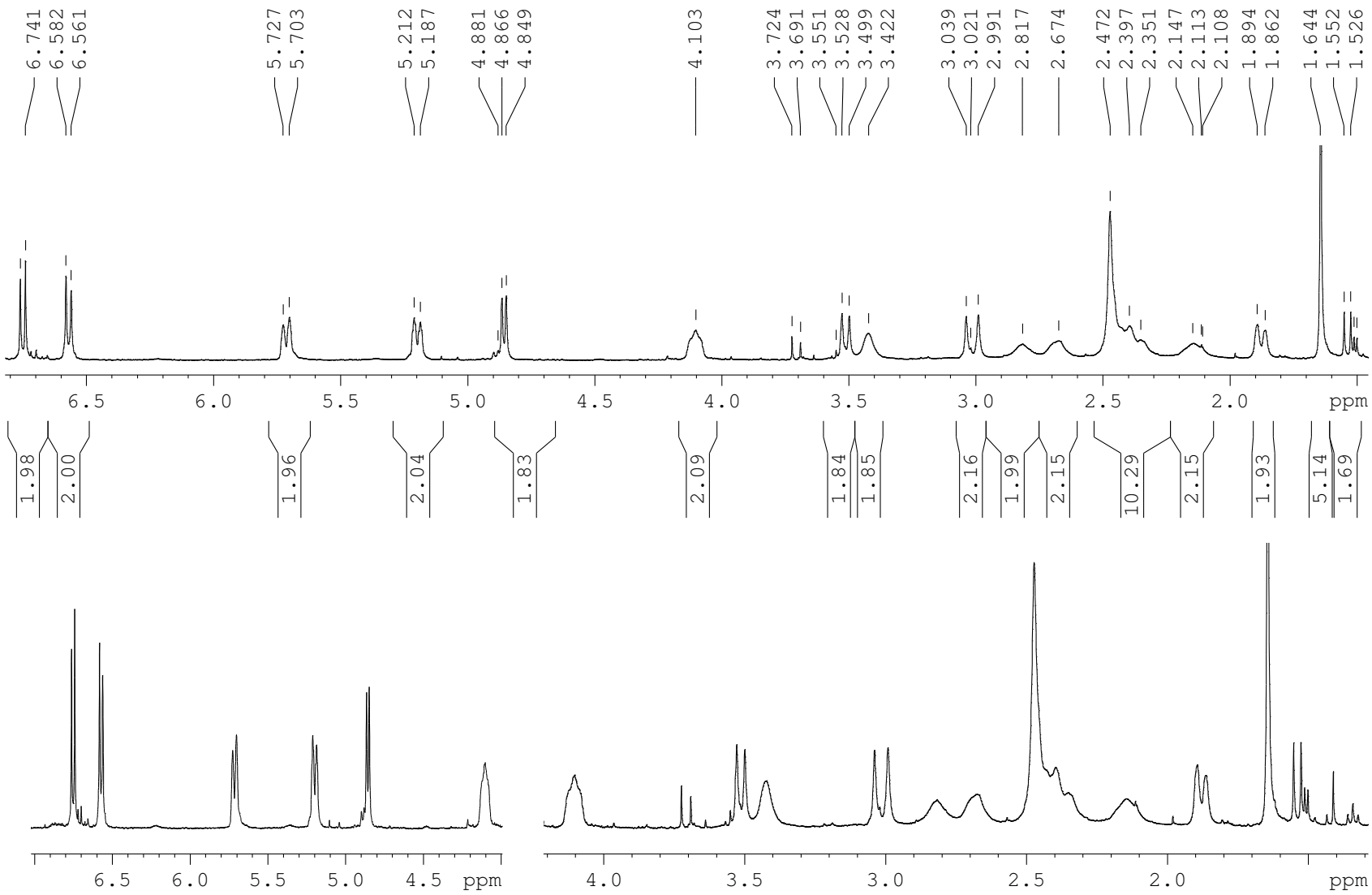


Compound: **372**

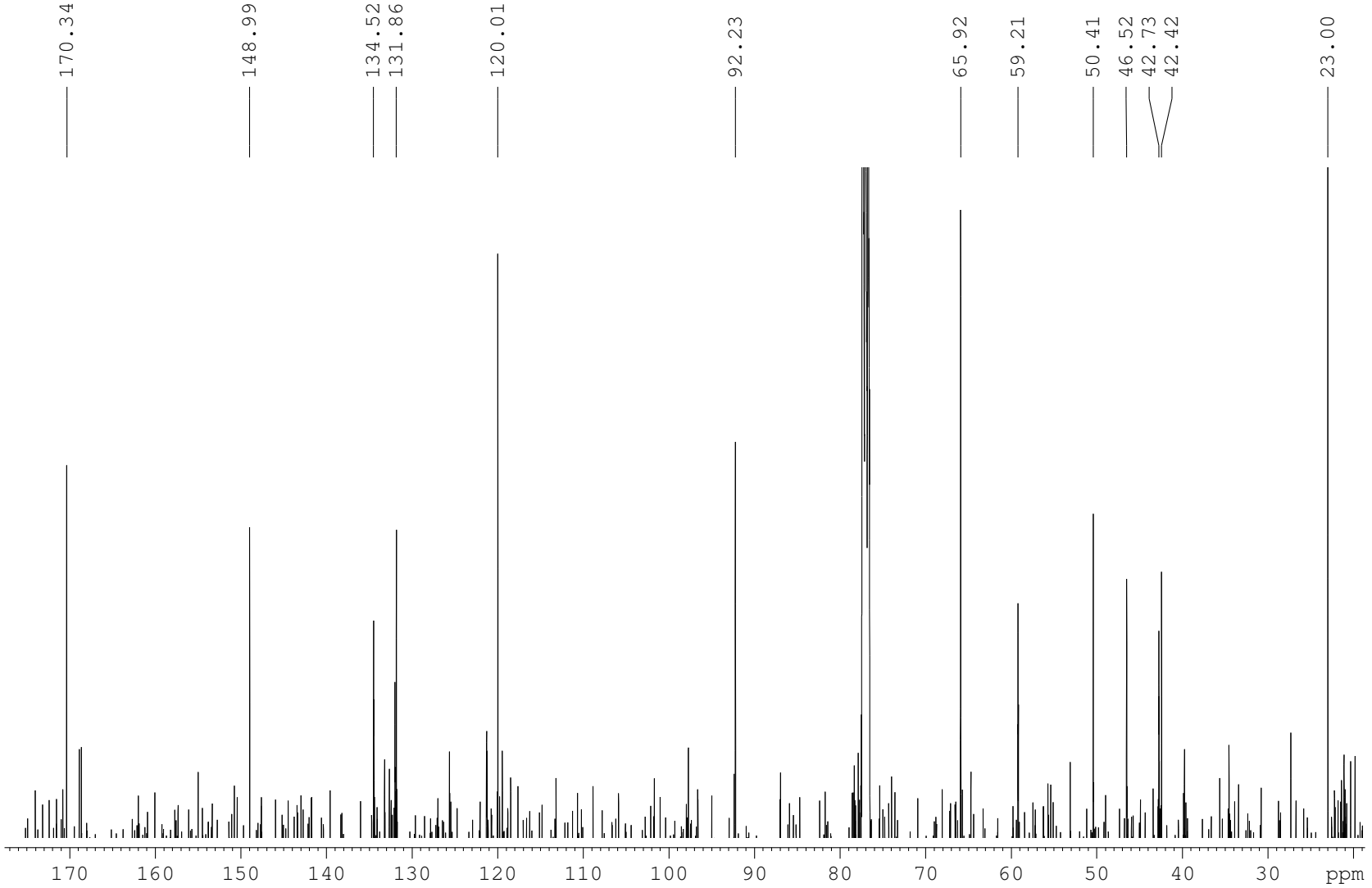
bis(3-morphinyl) 2,2-dimethylmalonate

^{1}H and ^{13}C NMR

Dimethyl opiate



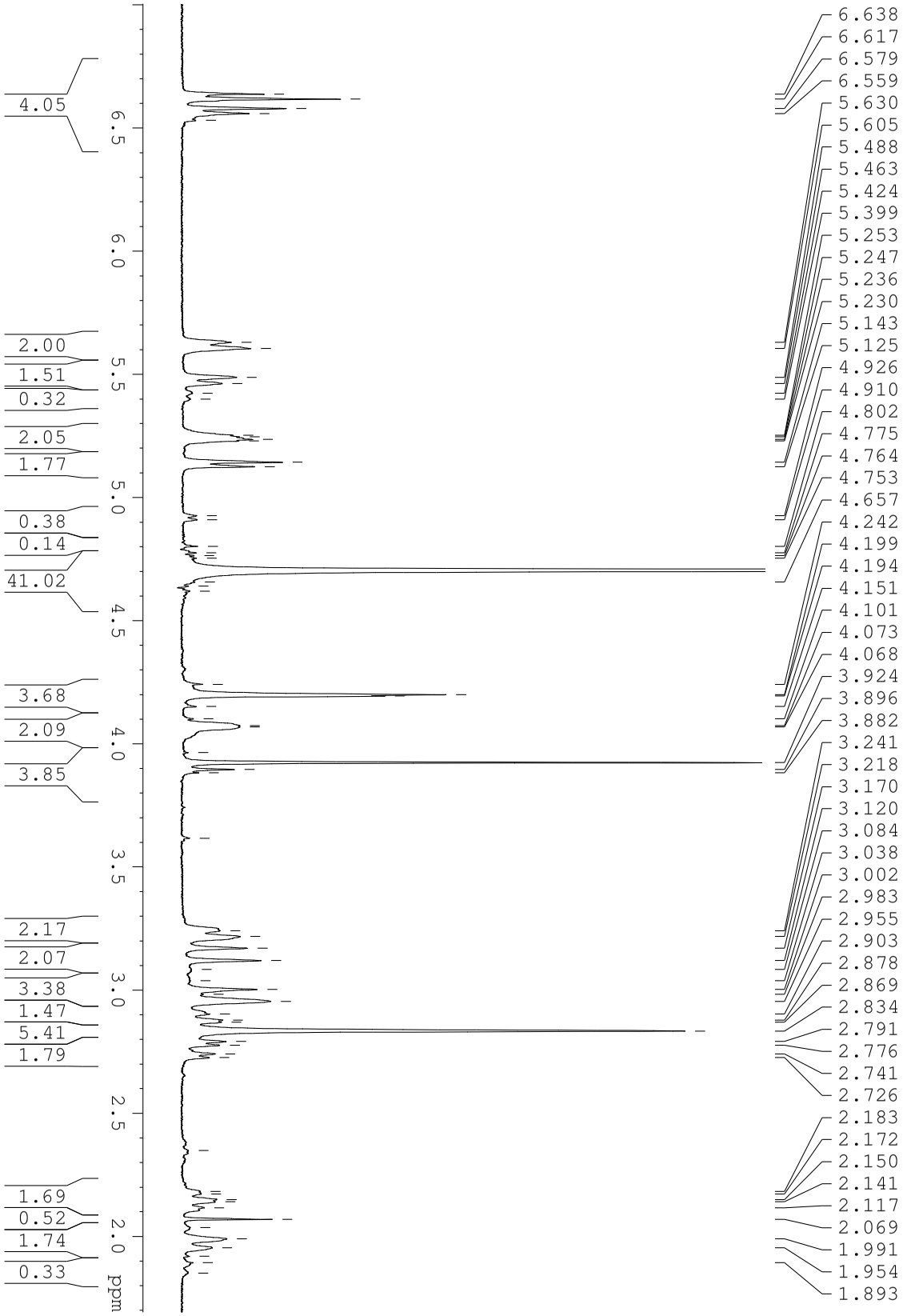
Dimethyl opiate



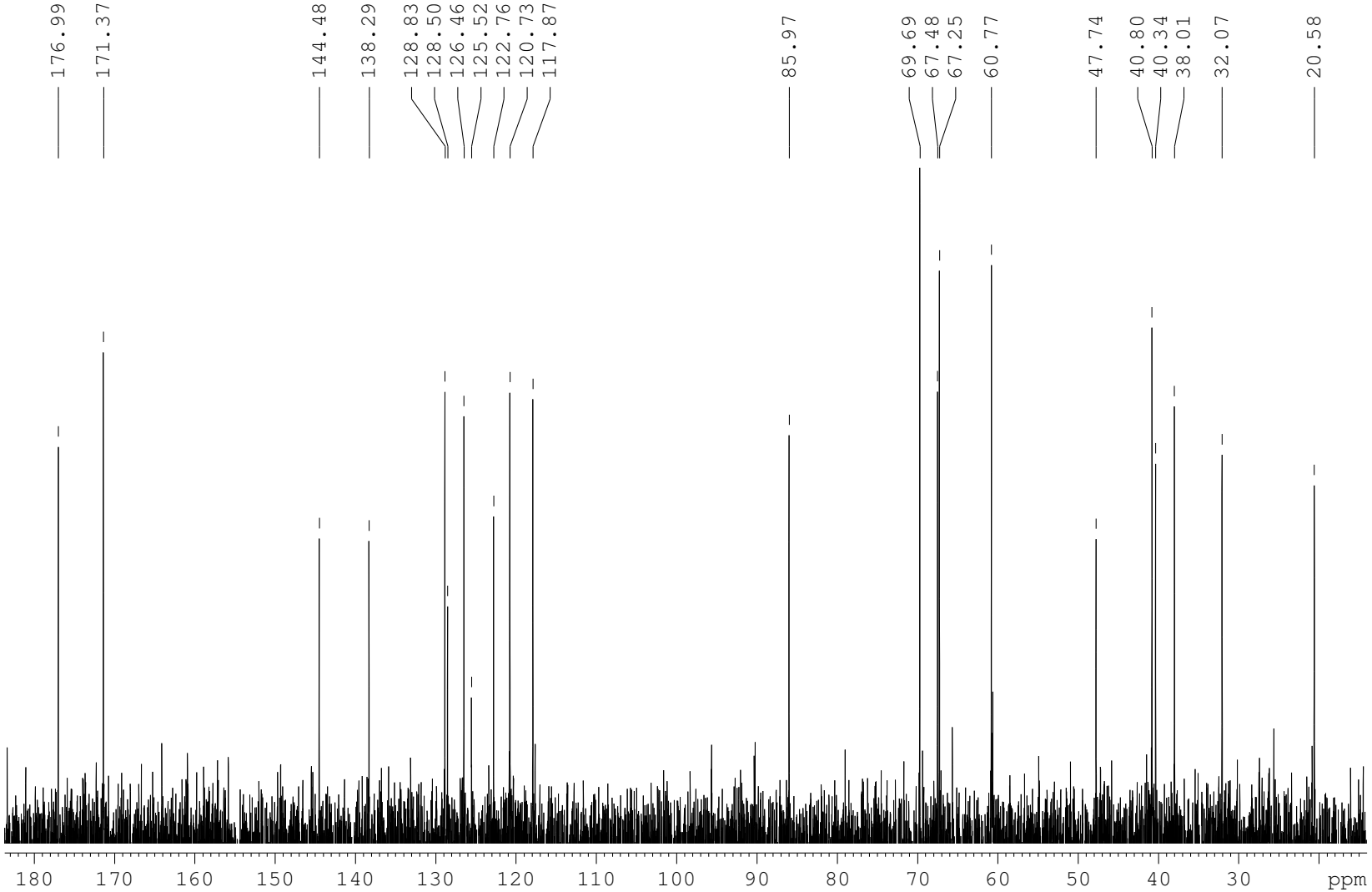
Compound: **373**

bis(3-morphinyl) diglycolate

^{1}H and ^{13}C NMR


4.05
2.00
1.51
0.32
2.05
1.77
0.38
0.14
41.02
3.68
2.09
3.85
2.17
2.07
3.38
1.47
5.41
1.79
1.69
0.52
1.74
0.33
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
6.638
6.617
6.579
6.559
5.630
5.605
5.488
5.463
5.424
5.399
5.253
5.247
5.236
5.230
5.143
5.125
4.926
4.910
4.802
4.775
4.764
4.753
4.657
4.242
4.199
4.194
4.151
4.101
4.073
4.068
3.924
3.896
3.882
3.241
3.218
3.170
3.120
3.084
3.038
3.002
2.983
2.955
2.903
2.878
2.869
2.834
2.791
2.776
2.741
2.726
2.183
2.172
2.150
2.141
2.117
2.069
1.991
1.954
1.893

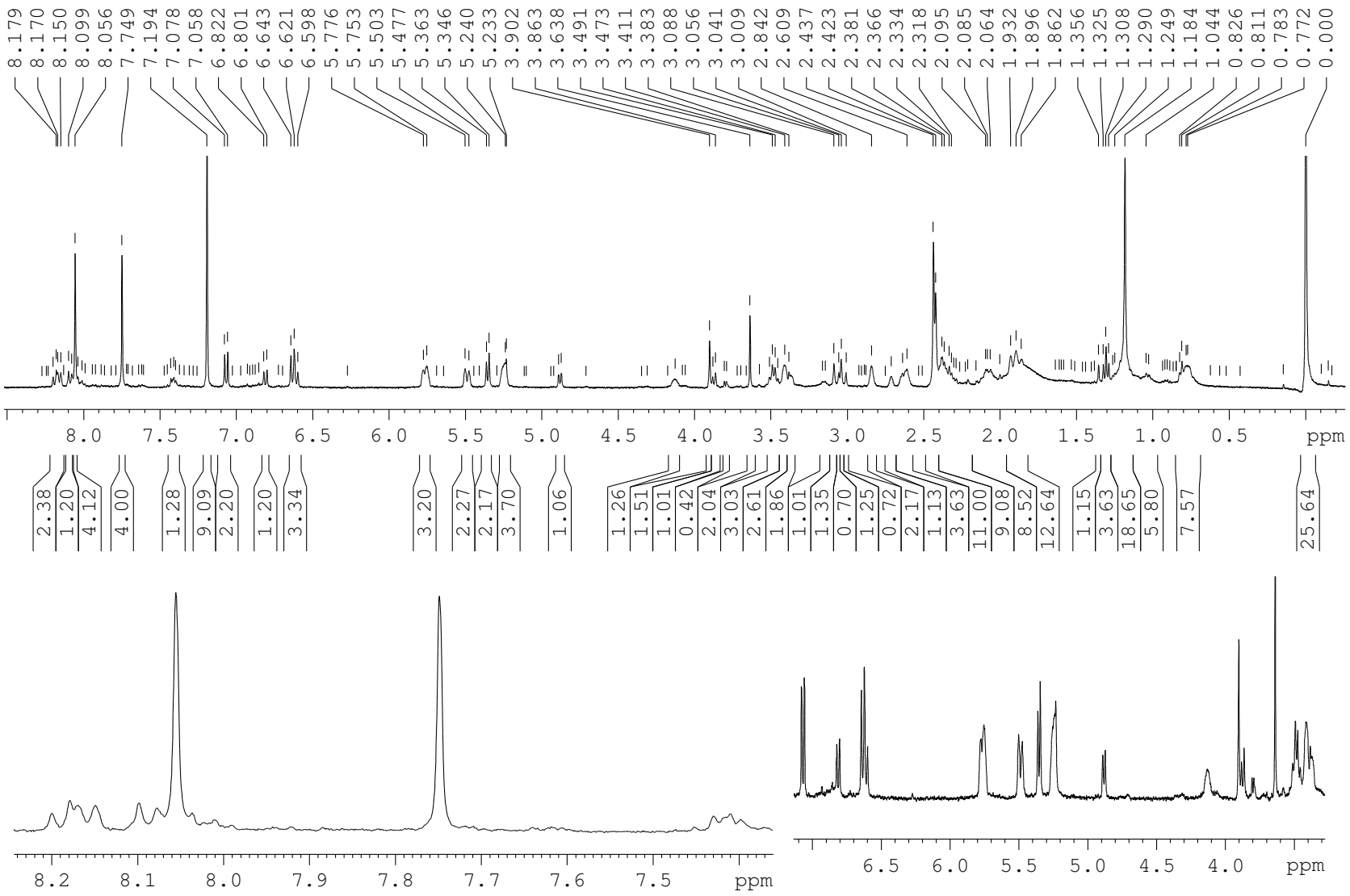
Diglycolyl Opiate

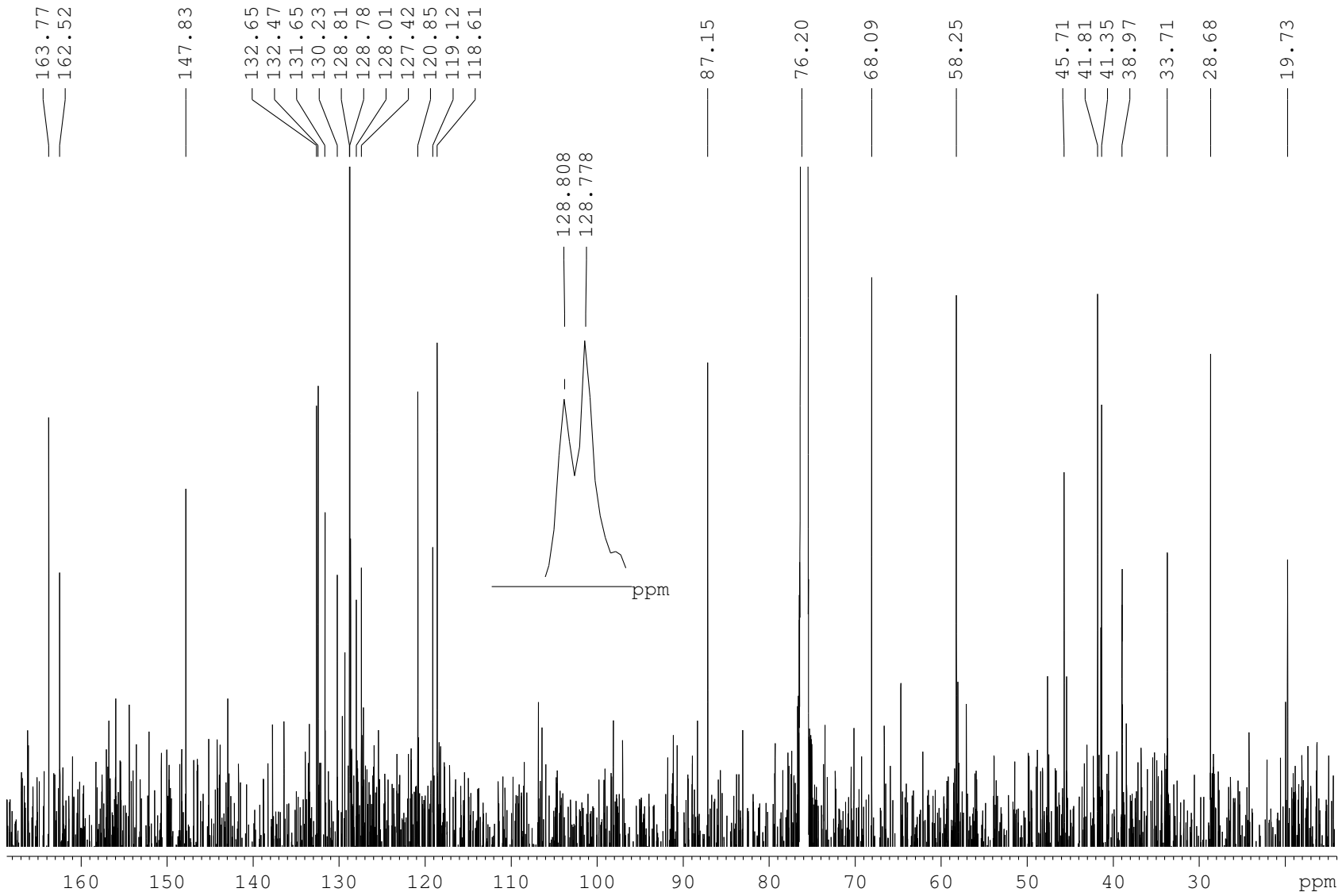


Compound: **380**

cyclo[3’-(6’-morphinyl terephthalate)(3-morphinyl)terephthalate]

^{1}H and ^{13}C NMR


8.179 8.170 8.150 8.099 8.056 7.749 7.194 7.078 7.058 6.822 6.801 6.643 6.621 6.598 5.776 5.753 5.503 5.477 5.363 5.346 5.240 5.233 3.902 3.863 3.638 3.491 3.473 3.411 3.383 3.088 3.056 3.041 3.009 2.842 2.609 2.437 2.423 2.381 2.366 2.334 2.318 2.095 2.085 2.064 1.932 1.896 1.862 1.356 1.325 1.308 1.290 1.249 1.184 1.044 0.826 0.811 0.783 0.772 0.000
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.38 1.20 4.12 4.00 1.28 9.09 2.20 1.20 3.34 3.20 2.27 2.17 3.70 1.06 1.26 1.51 1.01 0.42 2.04 3.03 2.61 1.86 1.01 1.35 0.70 1.25 0.72 2.17 1.13 3.63 11.00 9.08 8.52 12.64 1.15 3.63 18.65 5.80 7.57 25.64
8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 ppm
6.5 6.0 5.5 5.0 4.5 4.0 ppm

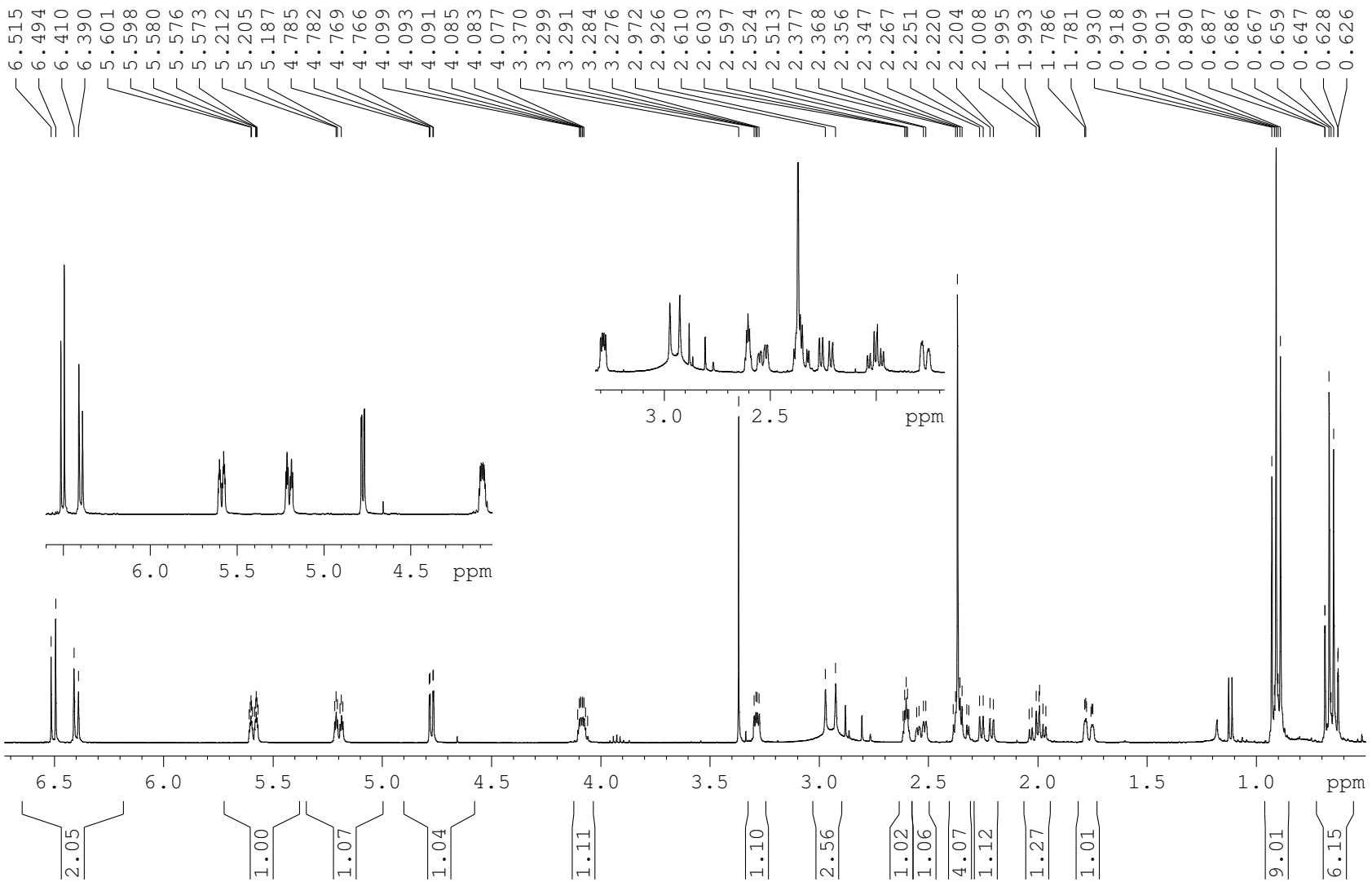

163.77
162.52
147.83
132.65
132.47
131.65
130.23
128.81
128.78
128.01
127.42
120.85
119.12
118.61
87.15
76.20
68.09
58.25
45.71
41.81
41.35
38.97
33.71
28.68
19.73
128.808
128.778
ppm
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

Compound: **396**

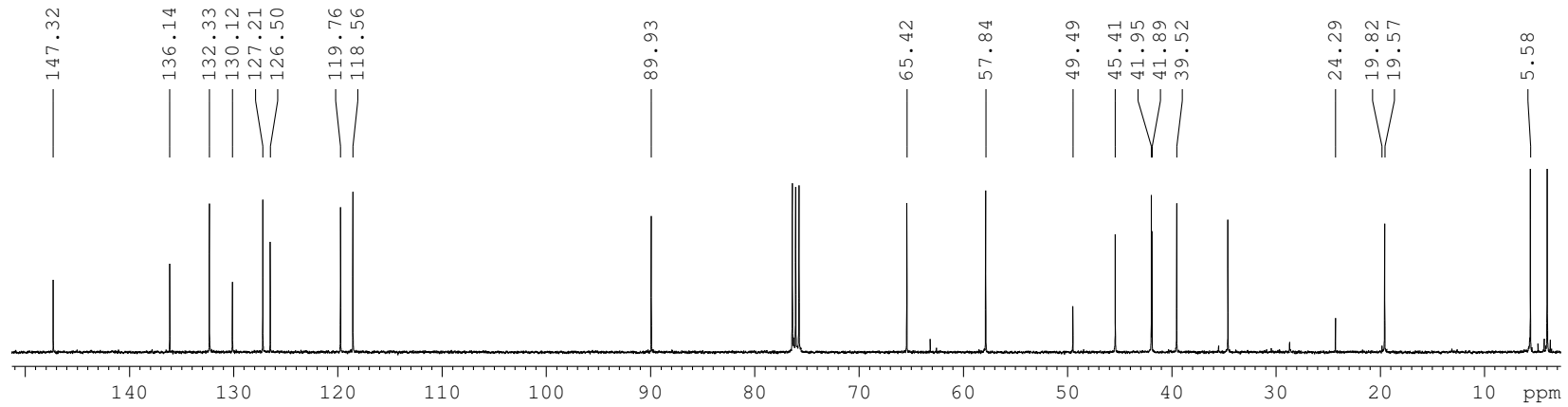
3-O-triethylsilyl morphine

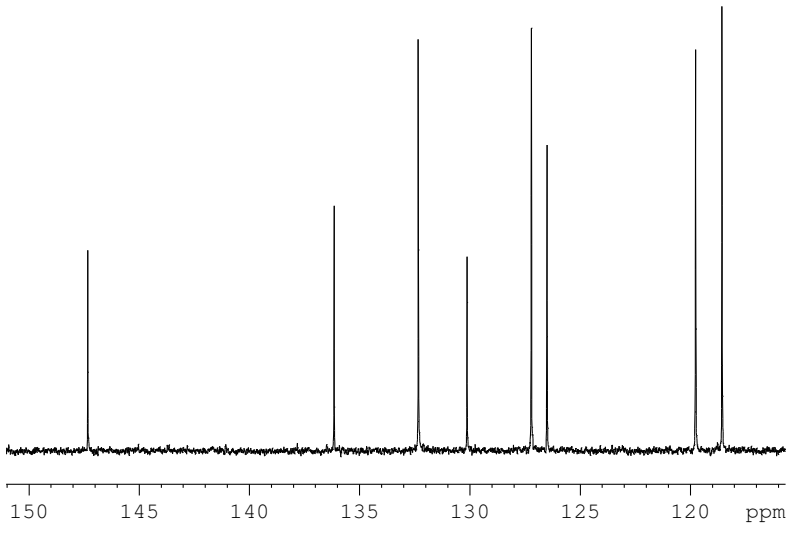
^{1}H and ^{13}C NMR

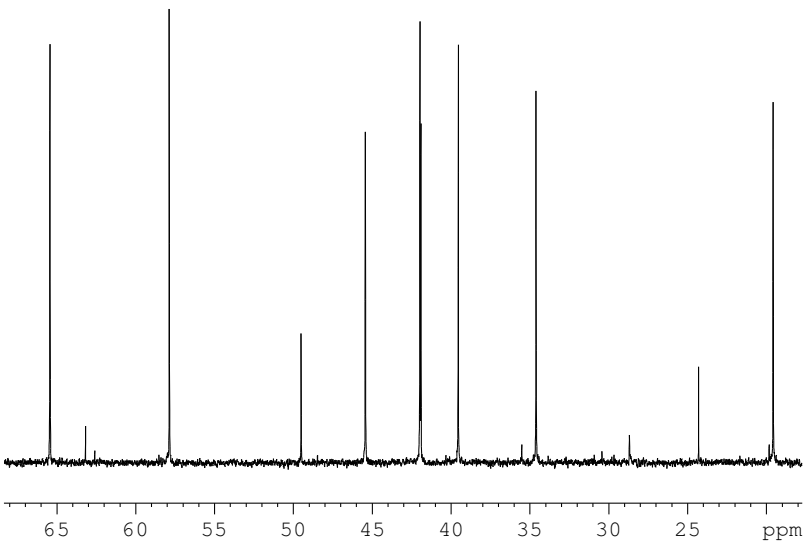
TES Morphine



TES Morphine







APPENDIX 2
X-Ray Crystallography Data